

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number  
**WO 01/16318 A2**

- (51) International Patent Classification?: C12N 15/12, C07K 14/47, 14/705, G01N 33/53, C12N 15/62, C07K 16/18 PCT/US00/04414 22 February 2000 (22.02.2000) US
- (21) International Application Number: PCT/US00/23328 PCT/US00/05601 1 March 2000 (01.03.2000) US
- (22) International Filing Date: 24 August 2000 (24.08.2000) 60/187,202 3 March 2000 (03.03.2000) US
- (25) Filing Language: English 60/191,007 21 March 2000 (21.03.2000) US
- (26) Publication Language: English PCT/US00/08439 30 March 2000 (30.03.2000) US
- (30) Priority Data: PCT/US99/20111 60/199,397 25 April 2000 (25.04.2000) US
- 1 September 1999 (01.09.1999) US PCT/US00/14042 22 May 2000 (22.05.2000) US
- PCT/US99/21090 60/209,832 5 June 2000 (05.06.2000) US
- 15 September 1999 (15.09.1999) US (71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- 7 December 1999 (07.12.1999) US (72) Inventors; and
- 9 December 1999 (09.12.1999) US (75) Inventors/Applicants (for US only): EATON, Dan, L. [US/US]; 75 Knight Drive, San Rafael, CA 94901 (US). FILVAROFF, Ellen [US/US]; 538 18th Avenue, San Francisco, CA 94121 (US). GERRITSEN, Mary, E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GODOWSKI, Paul, J. [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). GRIMALDI, Christopher, J. [US/US]; 1434 36th
- 11 January 2000 (11.01.2000) US
- PCT/US00/04341 18 February 2000 (18.02.2000) US
- PCT/US00/04342 18 February 2000 (18.02.2000) US

[Continued on next page]

(54) Title: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

<subunit 1 of 1, 266 aa, 1 stop  
<MW: 29766, pI: 8.39, NX(S/T): 0  
MWWFQQGLSFLPSALVIWTSAAFI FSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNIA  
AVLCIATIYVRYKQVHALSPEENVIIKLNKAGLVGLSCLGLSIVANFQKTTLFAAHVSGAV  
LTFGMGSLYMFVQTILSYQMOPKIHGKQVFWIRLLLVIWCGVSALSMLTCCSSVLHSGNFGTDL  
EQKLHWNPEDKGYVLHMITTAAEWSMSFSFSGFFLT YIRDFQKISLRVEANLHGLTLYDTAPC  
PINNERTRLLSRDI

**Important features:**

Type II transmembrane domain:  
amino acids 13-33

**Other Transmembrane domains:**

amino acids 54-73, 94-113, 160-180, 122-141

**N-myristoylation sites.**

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

(57) Abstract: The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

WO 01/16318 A2

## SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

### FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel DNA and to the  
5 recombinant production of novel polypeptides.

### BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and  
maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration,  
10 differentiation, or interaction with other cells, is typically governed by information received from other cells  
and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance,  
mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which  
are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted  
polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of  
15 action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics,  
biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons,  
interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins.  
Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts  
20 are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are  
focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel  
secreted proteins. Examples of screening methods and techniques are described in the literature [see, for  
example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation,  
25 differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation,  
migration, differentiation, or interaction with other cells, is typically governed by information received from  
other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides  
(for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and  
hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins.  
30 Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor  
kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like  
selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is  
regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze  
that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and

nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length,

amino acid sequence identity, alternatively at least about 84 % amino acid sequence identity, alternatively at least about 85 % amino acid sequence identity, alternatively at least about 86 % amino acid sequence identity, alternatively at least about 87 % amino acid sequence identity, alternatively at least about 88 % amino acid sequence identity, alternatively at least about 89 % amino acid sequence identity, alternatively at least about 90 % amino acid sequence identity, alternatively at least about 91 % amino acid sequence identity, alternatively at least about 92 % amino acid sequence identity, alternatively at least about 93 % amino acid sequence identity, alternatively at least about 94 % amino acid sequence identity, alternatively at least about 95 % amino acid sequence identity, alternatively at least about 96 % amino acid sequence identity, alternatively at least about 97 % amino acid sequence identity, alternatively at least about 98 % amino acid sequence identity and alternatively at least about 99 % amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By



Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO300 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA40625-1189".

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

5 Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO1864 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA45409-2511".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO1282 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA45495-1550".

10 Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO1063 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA49820-1427".

15 Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO1773 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA56406-1704".

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

20 Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO1013 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA56410-1414".

Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

25 Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO937 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA56436-1448".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO842 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA56855-1447".

30 Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO1180 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA56860-1510".

35 Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO831 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA56862-1343".

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO1069 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA59211-1450".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO1411 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA59212-1627".

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO1129 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA59213-1487".

Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO1027 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA59605-1418".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO1106 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA59609-1470".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO1291 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA59610-1556".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO3573 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA59837-2545".

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO3566 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA59844-2542".

Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO1098 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA59854-1459".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO1158 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA60625-1507".

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO1270 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA66308-1537".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

5 Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO1268 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA66519-1535".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO1327 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA66521-1583".

10 Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO1328 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA66658-1584".

15 Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO1329 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA66660-1585".

Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

20 Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO1340 cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA66663-1598".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

25 Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO1342 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA66674-1599".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO3579 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA68862-2546".

30 Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO1472 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA68866-1644".

35 Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO1461 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA68871-1638".

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO1566 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA77568-1626".

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

5 Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO1774 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA77626-1705".

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO1928 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA81754-2532".

10 Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO1865 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA81757-2512".

15 Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO1925 cDNA, wherein SEQ ID NO:133 is a clone designated herein as "DNA82302-2529".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

20 Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO1926 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA82340-2530".

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

25 Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA83500-2506".

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA84920-2614".

30 Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO3435 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA85066-2534".

35 Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO3543 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA86571-2551".

WO 01/16318

Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO20233 cDNA, wherein SEQ ID NO:163 is a clone designated herein as "DNA165608".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

Figure 165 shows a nucleotide sequence (SEQ ID NO:165) of a native sequence PRO19670 cDNA, wherein SEQ ID NO:165 is a clone designated herein as "DNA131639-2874".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1890 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA79230-2525".

Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

#### I. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino

sequence identity, alternatively at least about 91 % amino acid sequence identity, alternatively at least about 92 % amino acid sequence identity, alternatively at least about 93 % amino acid sequence identity, alternatively at least about 94 % amino acid sequence identity, alternatively at least about 95 % amino acid sequence identity, alternatively at least about 96 % amino acid sequence identity, alternatively at least about 97 % amino acid sequence identity, alternatively at least about 98 % amino acid sequence identity and alternatively at least about 99 % amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction  $X/Y$ .

where  $X$  is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where  $Y$  is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous



complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995):

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any

forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')<sub>2</sub> fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V<sub>H</sub>-V<sub>L</sub> dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')<sub>2</sub> antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA<sub>1</sub>, and IgA<sub>2</sub>.

"Single-chain Fv" or "sFv" antibody fragments comprise the V<sub>H</sub> and V<sub>L</sub> domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) in the same polypeptide chain (V<sub>H</sub>-V<sub>L</sub>). By using a linker that is too short to allow pairing between the two domains

Table 1

```

/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
5  * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define _M      -8      /* value of a match with a stop */

10 int      _day[26][26] = {
/*      A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */      { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */      { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */      {-2, -4, 15, -5, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
15 /* D */      { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */      { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */      {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */      { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */      {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
20 /* I */      {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */      { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */      {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */      {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */      {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
25 /* N */      { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */      {_M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */      { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */      { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */      {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
30 /* S */      { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */      { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */      { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */      { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */      {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
35 /* X */      { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */      {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */      { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

40

45

50

55

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
5 * The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10 * Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

20 static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
25 1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                main
30     int      ac;
     char      *av[ ];
{
    prog = av[0];
    if (ac != 3) {
35         fprintf(stderr, "usage: %s file1 file2\n", prog);
         fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
         fprintf(stderr, "The sequences can be in upper- or lower-case\n");
         fprintf(stderr, "Any lines beginning with ';', '>' or '<' are ignored\n");
         fprintf(stderr, "Output is in the file \"align.out\"\n");
         exit(1);
40     }
     namex[0] = av[1];
     namex[1] = av[2];
     seqx[0] = getseq(namex[0], &len0);
     seqx[1] = getseq(namex[1], &len1);
45     xbm = (dna)? _dbval : _pbval;

     endgaps = 0;                                /* 1 to penalize endgaps */
     ofile = "align.out";                        /* output file */

50     nw();                                /* fill in the matrix, get the possible jumps */
     readjumps();                                /* get the actual jumps */
     print();                                /* print stats, alignment */

55     cleanup(0);                                /* unlink any tmp files */
}

```

Table 1 (cont')

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
5  * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array pl[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
10 * nums() -- put out a number line: dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

15 #include "nw.h"

#define SPC 3
#define P_LINE 256 /* maximum output line */
20 #define P_SPC 3 /* space between name or num and seq */

extern _day[26][26];
int olen; /* set output line length */
FILE *fx; /* output file */

25 print()
{
    int lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
30         fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "< first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "< second sequence: %s (length = %d)\n", namex[1], len1);
35     olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
40         pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
45         lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
50     }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
55     }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

60

```

print

Table 1 (cont')

...getmat

```

5      fprintf(fx, "< gaps in first sequence: %d", gapx);
      if (gapx) {
          (void) sprintf(outx, " (%d %s%s)",
              ngapx, (dna)? "base": "residue", (ngapx == 1)? "" : "s");
          fprintf(fx, "%s", outx);

      fprintf(fx, ", gaps in second sequence: %d", gapy);
10     if (gapy) {
          (void) sprintf(outx, " (%d %s%s)",
              ngapy, (dna)? "base": "residue", (ngapy == 1)? "" : "s");
          fprintf(fx, "%s", outx);
      }
15     if (dna)
          fprintf(fx,
              "\n< score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
              smax, DMAT, DMIS, DINS0, DINS1);
      else
20         fprintf(fx,
              "\n< score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
              smax, PINS0, PINS1);
      if (endgaps)
          fprintf(fx,
25             "< endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
              firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
              lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
      else
          fprintf(fx, "< endgaps not penalized\n");
30 }

static      nm;          /* matches in core -- for checking */
static      lmax;        /* lengths of stripped file names */
static      ij[2];       /* jmp index for a path */
static      nc[2];       /* number at start of current line */
35 static      ni[2];      /* current elem number -- for gapping */
static      siz[2];
static char  *ps[2];      /* ptr to current element */
static char  *po[2];      /* ptr to next output char slot */
static char  out[2][P_LINE]; /* output line */
40 static char  star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp [ ]
 */
45 static
pr_align()
{
    int      nn;          /* char count */
    int      more;
50     register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(name[i]);
        if (nn > lmax)
55             lmax = nn;

        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
60         po[i] = out[i];
    }

```

pr\_align

Table 1 (cont')

...dumpblock

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
                  stars();
10             putline(i);
              if (i == 0 && *out[1])
                  fprintf(fx, star);
              if (i == 1)
                  nums(i);
15         }
    }

/*
20  * put out a number line: dumpblock()
  */
  static
  nums(ix)                                nums
  {
      int      ix;      /* index in out[] holding seq line */
25      {
          char      nline[P_LINE];
          register   i, j;
          register char *pn, *px, *py;

30      for (pn = nline, i = 0; i < lmax + P_SPC; i++, pn++)
          *pn = ' ';
          for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
              if (*py == ' ' || *py == '-')
                  *pn = ' ';
35              else {
                  if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                      j = (i < 0)? -i : i;
                      for (px = pn; j /= 10, px--)
                          *px = j%10 + '0';
40                      if (i < 0)
                          *px = '-';

                      }
                      else
                          *pn = ' ';
45                      i++;
                  }
              }
          *pn = '\0';
          nc[ix] = i;
          for (pn = nline; *pn; pn++)
              (void) putc(*pn, fx);
          (void) putc('\n', fx);
50      }

/*
55  * put out a line (name, [num], seq, [num]): dumpblock()
  */
  static
  putline(ix)                                putline
  {
      int      ix;
60      {

```



Table 1 (cont')

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
5 stripname(pn)
    char *pn; /* file name (may be path) */
{
    register char *px, *py;
10    py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
15    if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}
20
```

stripname

'Table 1 (cont')

...getseq

```

py = pseq + 4;
*len = tlen;
rewind(fp);
5
while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++) {
10        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
        if (index("ATGCU", *(py-1)))
            natgc++;
15    }
}
*py++ = '\0';
*py = '\0';
(void) fclose(fp);
dna = natgc > (tlen/3);
return(pseq+4);
20
}

25 char *
g_alloc(msg, nx, sz)                                g_alloc
    char *msg; /* program, calling routine */
    int nx, sz; /* number and size of elements */
{
30     char *px, *calloc();

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
35             fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
40 }

/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()
45 {
    int fd = -1;
    int siz, i0, i1;
    register i, j, xx;

50     if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
            fprintf(stderr, "%s: can't open() %s\n", prog, jname);
            cleanup(1);
55         }
    }
    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; i++) {
        while (1) {
60             for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)

```

Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5  writejumps(ix)                                     writejumps
    int    ix;
    {
        char    *mktemp();
10         if (!fj) {
            if (mktemp(jname) < 0) {
                fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                cleanup(1);
            }
15         if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
20         }
        (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
    }
25
30
35
40
45
50
55
60

```

Table 3

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

5    % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

10    5 divided by 10 = 50%

Table 5

PRO-DNA	NNNNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

5    % nucleic acid sequence identity =

... (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10    4 divided by 12 = 33.3%

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

5 PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired  
10 termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial  
15 changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

### C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparagyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the

#### D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., **85**:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

##### 1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like <sup>32</sup>P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.



*ilvG kan<sup>r</sup>*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylophilic Yeasts, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

### 3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally

promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a PRO "knock out" animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of

analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN<sup>TM</sup>, PLURONICS<sup>TM</sup> or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In Toxicokinetics and New Drug Development, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 µg/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991).

polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Diagnostic and therapeutic uses of the herein disclosed molecules may also be based upon the positive functional assay hits disclosed and described below.

#### F. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

##### 1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., *supra*] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

### 3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones



pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., **176**: 1191-1195 (1992) and Shopes, J. Immunol., **148**: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, **53**: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, **3**: 219-230 (1989).

#### 7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include  $^{212}\text{Bi}$ ,  $^{131}\text{I}$ ,  $^{131}\text{In}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

#### 8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030 (1980); and U.S. Pat. Nos.

acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

#### G. Uses for anti-PRO Antibodies

The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, *e.g.*, detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as <sup>3</sup>H, <sup>14</sup>C, <sup>32</sup>P, <sup>35</sup>S, or <sup>125</sup>I, a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such as Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLE 2: Isolation of cDNA clones by Amylase Screening1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System).

5 In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the Sall/NotI linker cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

2. Preparation of random primed cDNA library

10 A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linker with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI

15 cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

20

3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was

25 added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

30 The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL<sup>+</sup>, SUC<sup>+</sup>, GAL<sup>+</sup>. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*, *sec62*, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins

35

#### 4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30  $\mu$ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5  $\mu$ l) was used as a template for the PCR reaction in a 25  $\mu$ l volume containing: 0.5  $\mu$ l KlenTaq (Clontech, Palo Alto, CA); 4.0  $\mu$ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5  $\mu$ l KlenTaq buffer (Clontech); 0.25  $\mu$ l forward oligo 1; 0.25  $\mu$ l reverse oligo 2; 12.5  $\mu$ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:169)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:170)

PCR was then performed as follows:

a.	Denature	92°C, 5 minutes
b.	3 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	59°C, 30 seconds
	Extend	72°C, 60 seconds
c.	3 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	57°C, 30 seconds
	Extend	72°C, 60 seconds
d.	25 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	55°C, 30 seconds
	Extend	72°C, 60 seconds
e.	Hold	4°C

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5  $\mu$ l) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., *supra*. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

#### EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine

Table 7 (cont')

	DNA60625-1507	209975	June 16, 1998
	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203112	August 11, 1998
5	DNA62812-1594	203248	September 9, 1998
	DNA62815-1576	203247	September 9, 1998
	DNA64881-1602	203240	September 9, 1998
	DNA64886-1601	203241	September 9, 1998
	DNA64902-1667	203317	October 6, 1998
10	DNA64950-1590	203224	September 15, 1998
	DNA65403-1565	203230	September 15, 1998
	DNA66308-1537	203159	August 25, 1998
	DNA66519-1535	203236	September 15, 1998
	DNA66521-1583	203225	September 15, 1998
15	DNA66658-1584	203229	September 15, 1998
	DNA66660-1585	203279	September 22, 1998
	DNA66663-1598	203268	September 22, 1998
	DNA66674-1599	203281	September 22, 1998
	DNA68862-2546	203652	February 9, 1999
20	DNA68866-1644	203283	September 22, 1998
	DNA68871-1638	203280	September 22, 1998
	DNA68880-1676	203319	October 6, 1998
	DNA68883-1691	203535	December 15, 1998
	DNA68885-1678	203311	October 6, 1998
25	DNA71277-1636	203285	September 22, 1998
	DNA73727-1673	203459	November 3, 1998
	DNA73734-1680	203363	October 20, 1998
	DNA73735-1681	203356	October 20, 1998
	DNA76393-1664	203323	October 6, 1998
30	DNA77301-1708	203407	October 27, 1998
	DNA77568-1626	203134	August 18, 1998
	DNA77626-1705	203536	December 15, 1998
	DNA81754-2532	203542	December 15, 1998
	DNA81757-2512	203543	December 15, 1998
35	DNA82302-2529	203534	December 15, 1998
	DNA82340-2530	203547	December 22, 1998
	DNA83500-2506	203391	October 29, 1998
	DNA84920-2614	203966	April 27, 1999
	DNA85066-2534	203588	January 12, 1999
40	DNA86571-2551	203660	February 9, 1999
	DNA87991-2540	203656	February 9, 1999
	DNA92238-2539	203602	January 20, 1999
	DNA96042-2682	PTA-382	July 20, 1999
	DNA96787-2534	203589	January 12, 1999
45	DNA125185-2806	PTA-1031	December 7, 1999
	DNA147531-2821	PTA-1185	January 11, 2000
	DNA115291-2681	PTA-202	June 8, 1999
	DNA164625-28890	PTA-1535	March 21, 2000
	DNA131639-2874	PTA-1784	April 25, 2000
50	DNA79230-2525	203549	December 22, 1998

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate•2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

*E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The

serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompanyrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700  $\mu$ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5  $\mu$ g/ml bovine insulin and 0.1  $\mu$ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as  $\text{CaPO}_4$  or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as  $^{35}\text{S}$ -methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by  $\text{Ni}^{2+}$ -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.



**EXAMPLE 8: Expression of PRO in Yeast**

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

**EXAMPLE 9: Expression of PRO in Baculovirus-Infected Insect Cells**

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (PharMingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm

affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 11: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 12: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with

WO 01/16318

antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

#### EXAMPLE 14: Pericyte c-Fos Induction (Assay 93)

This assay shows that certain polypeptides of the invention act to induce the expression of c-fos in pericyte cells and, therefore, are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. Induction of c-fos expression in pericytes is also indicative of the induction of angiogenesis and, as such, PRO polypeptides capable of inducing the expression of c-fos would be expected to be useful for the treatment of conditions where induced angiogenesis would be beneficial including, for example, wound healing, and the like. Specifically, on day 1, pericytes are received from VEC Technologies and all but 5 ml of media is removed from flask. On day 2, the pericytes are trypsinized, washed, spun and then plated onto 96 well plates. On day 7, the media is removed and the pericytes are treated with 100  $\mu$ l of PRO polypeptide test samples and controls (positive control = DME+5% serum +/- PDGF at 500 ng/ml; negative control = protein 32). Replicates are averaged and SD/CV are determined. Fold increase over Protein 32 (buffer control) value indicated by chemiluminescence units (RLU) luminometer reading verses frequency is plotted on a histogram. Two-fold above Protein 32 value is considered positive for the assay. ASY Matrix: Growth media = low glucose DMEM = 20% FBS + 1X pen strep + 1X fungizone. Assay Media = low glucose DMEM +5% FBS.

The following polypeptides tested positive in this assay: PRO1347 and PRO1340.

#### EXAMPLE 15: Ability of PRO Polypeptides to Stimulate the Release of Proteoglycans from Cartilage (Assay 97)

The ability of various PRO polypeptides to stimulate the release of proteoglycans from cartilage tissue was tested as follows.

The metacarpophalangeal joint of 4-6 month old pigs was aseptically dissected, and articular cartilage was removed by free hand slicing being careful to avoid the underlying bone. The cartilage was minced and cultured in bulk for 24 hours in a humidified atmosphere of 95% air, 5% CO<sub>2</sub> in serum free (SF) media (DME/F12 1:1) with 0.1% BSA and 100U/ml penicillin and 100 $\mu$ g/ml streptomycin. After washing three times, approximately 100 mg of articular cartilage was aliquoted into micronics tubes and incubated for an additional 24 hours in the above SF media. PRO polypeptides were then added at 1% either alone or in combination with 18 ng/ml interleukin-1 $\alpha$ , a known stimulator of proteoglycan release from cartilage tissue.

The following PRO polypeptides tested positive in this assay: PRO263, PRO295, PRO1282, PRO1063, PRO1356, PRO3543, and PRO5990.

EXAMPLE 18: Tumor Versus Normal Differential Tissue Expression Distribution

Oligonucleotide probes were constructed from some of the PRO polypeptide-encoding nucleotide sequences shown in the accompanying figures for use in quantitative PCR amplification reactions. The oligonucleotide probes were chosen so as to give an approximately 200-600 base pair amplified fragment from the 3' end of its associated template in a standard PCR reaction. The oligonucleotide probes were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in the various tumor and normal tissues tested.  $\beta$ -actin was used as a control to assure that equivalent amounts of nucleic acid was used in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results.

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
20	DNA26843-1389	normal lung rectum tumor	lung tumor normal rectum
	DNA30867-1335	normal kidney	kidney tumor
25	DNA40621-1440	normal lung	lung tumor
	DNA40625-1189	normal lung	lung tumor
	DNA45409-2511	melanoma tumor	normal skin
30	DNA56406-1704	kidney tumor normal skin	normal kidney melanoma tumor
	DNA56410-1414	normal stomach	stomach tumor
35	DNA56436-1448	normal skin	melanoma tumor
	DNA56855-1447	normal esophagus rectum tumor	esophageal tumor normal rectum
40	DNA56860-1510	normal kidney rectum tumor	kidney tumor normal rectum
45	DNA56862-1343	kidney tumor normal lung	normal kidney lung tumor

WO 01/16318

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
	DNA61755-1554	normal stomach kidney tumor	stomach tumor normal kidney
5	DNA62812-1594	normal stomach normal lung normal rectum normal skin	stomach tumor lung tumor rectum tumor melanoma tumor
10	DNA62815-1576	esophageal tumor	normal esophagus
	DNA64881-1602	normal stomach normal lung	stomach tumor lung tumor
15	DNA64902-1667	esophageal tumor kidney tumor	normal esophagus normal kidney
	DNA65403-1565	normal esophagus	esophageal tumor
20	DNA66308-1537	normal lung	lung tumor
	DNA66519-1535	kidney tumor	normal kidney
25	DNA66521-1583	normal esophagus normal stomach normal lung normal rectum normal skin	esophageal tumor stomach tumor lung tumor rectum tumor melanoma tumor
30	DNA66658-1584	normal lung melanoma tumor	lung tumor normal skin
	DNA66660-1585	lung tumor	normal lung
35	DNA66674-1599	kidney tumor normal lung	normal kidney lung tumor
	DNA68862-2546	melanoma tumor	normal skin
40	DNA68866-1644	normal stomach	stomach tumor
	DNA68871-1638	lung tumor normal skin	normal lung melanoma tumor
45	DNA68880-1676	normal lung normal skin	lung tumor melanoma tumor
	DNA68883-1691	esophageal tumor	normal esophagus
50	DNA68885-1678	lung tumor	normal lung
	DNA71277-1636	normal stomach	stomach tumor
55	DNA73734-1680	normal lung	lung tumor

The assay is performed as follows. A PRO polypeptide of the present invention suspected of being a ligand for a receptor is expressed as a fusion protein containing the Fc domain of human IgG (an immunoadhesin). Receptor-ligand binding is detected by allowing interaction of the immunoadhesin polypeptide with cells (e.g. Cos cells) expressing candidate PRO polypeptide receptors and visualization of bound immunoadhesin with fluorescent reagents directed toward the Fc fusion domain and examination by microscope.

- 5 Cells expressing candidate receptors are produced by transient transfection, in parallel, of defined subsets of a library of cDNA expression vectors encoding PRO polypeptides that may function as receptor molecules. Cells are then incubated for 1 hour in the presence of the PRO polypeptide immunoadhesin being tested for possible receptor binding. The cells are then washed and fixed with paraformaldehyde. The cells are then incubated with fluorescent conjugated antibody directed against the Fc portion of the PRO polypeptide immunoadhesin (e.g. FITC conjugated goat anti-human-Fc antibody). The cells are then washed again and examined by microscope. A positive interaction is judged by the presence of fluorescent labeling of cells transfected with cDNA encoding a particular PRO polypeptide receptor or pool of receptors and an absence of similar fluorescent labeling of similarly prepared cells that have been transfected with other cDNA or pools of cDNA. If a defined pool of cDNA expression vectors is judged to be positive for interaction with a PRO polypeptide immunoadhesin, the individual cDNA species that comprise the pool are tested individually (the pool is "broken down") to determine the specific cDNA that encodes a receptor able to interact with the PRO polypeptide immunoadhesin.

- In another embodiment of this assay, an epitope-tagged potential ligand PRO polypeptide (e.g. 8 histidine "His" tag) is allowed to interact with a panel of potential receptor PRO polypeptide molecules that have been expressed as fusions with the Fc domain of human IgG (immunoadhesins). Following a 1 hour co-incubation with the epitope tagged PRO polypeptide, the candidate receptors are each immunoprecipitated with protein A beads and the beads are washed. Potential ligand interaction is determined by western blot analysis of the immunoprecipitated complexes with antibody directed towards the epitope tag. An interaction is judged to occur if a band of the anticipated molecular weight of the epitope tagged protein is observed in the western blot analysis with a candidate receptor, but is not observed to occur with the other members of the panel of potential receptors.

Using these assays, the following receptor/ligand interactions have been herein identified:

- (1) PRO10272 binds to PRO5801.
- (2) PRO20110 binds to the human IL-17 receptor (Yao et al., *Cytokine* 9(11):794-800 (1997); also herein designated as PRO1) and to PRO20040.
- 30 (3) PRO10096 binds to PRO20233.
- (4) PRO19670 binds to PRO1890.

- The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the

WHAT IS CLAIMED IS:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) and Figure 168 (SEQ ID NO:168).

2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure

Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165) and Figure 167 (SEQ ID NO:167).

4. Isolated nucleic acid having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5. A vector comprising the nucleic acid of Claim 1.

6. The vector of Claim 5 operably linked to control sequences recognized by a host cell transformed with the vector.

7. A host cell comprising the vector of Claim 5.

8. The host cell of Claim 7, wherein said cell is a CHO cell.

9. The host cell of Claim 7, wherein said cell is an *E. coli*.

10. The host cell of Claim 7, wherein said cell is a yeast cell.

11. A process for producing a PRO polypeptides comprising culturing the host cell of Claim 7 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102



58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156),

(SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

(b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure

23. The method according to Claim 21, wherein said E, F, G, H or I polypeptide is labeled with a detectable label.

24. The method according to Claim 21, wherein said E, F, G, H or I polypeptide is attached to a solid support.

5

25. A method of detecting a polypeptide designated as E, F, G, H or I in a sample suspected of containing an E, F, G, H or I polypeptide, said method comprising contacting said sample with a polypeptide designated herein as A, B, C or D and determining the formation of a A/E, B/F, B/G, C/H or D/I polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of an A, B, C or D polypeptide in said sample and wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

10

26. The method according to Claim 25, wherein said sample comprises cells suspected of expressing said E, F, G, H or I polypeptide.

15

27. The method according to Claim 25, wherein said A, B, C or D polypeptide is labeled with a detectable label.

20

28. The method according to Claim 25, wherein said A, B, C or D polypeptide is attached to a solid support.

25

29. A method of linking a bioactive molecule to a cell expressing a polypeptide designated as A, B, C or D, said method comprising contacting said cell with a polypeptide designated as E, F, G, H or I that is bound to said bioactive molecule and allowing said A, B, C or D and said E, F, G, H or I polypeptides to bind to one another, thereby linking said bioactive molecules to said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

30

30. The method according to Claim 29, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

35

31. The method according to Claim 29, wherein said bioactive molecule causes the death of said cell.

1/168

**FIGURE 1**

GGGGCTTCGGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGGATTTACAAAAGGTGCAGGTA  
TGAGCAGGTCTGAAGACTAACATTTTGTGAAGTTGTAAAACAGAAAACCTGTTAGAAATGTGG  
TGGTTTCAGCAAGGCCTCAGTTTTCCTTCCTTCAGCCCTTGTAATTTGGACATCTGCTGCTTTC  
ATATTTTCATACATTACTGCAGTAACACTCCACCATATAGACCCGGCTTTACCTTATATCAGT  
GACACTGGTACAGTAGCTCCAGAAAAATGCTTATTTGGGGCAATGCTAAATATTGCGGCAGTT  
TTATGCATTGCTACCATTTATGTTTCGTTATAAGCAAGTTCATGCTCTGAGTCCTGAAGAGAAC  
GTTATCATCAAATTAACAAGGCTGGCCTTGTAAGTGGAGCTGTGCTTACC  
ATTGTGGCAAACCTTCAGAAAAACAACCCTTTTTGCTGCACATGTAAGTGGAGCTGTGCTTACC  
TTTGGTATGGGCTCATTATATATGTTTGTTTCAGACCATCCTTTCCTACCAAATGCAGCCCCAA  
ATCCATGGCAAACAAGTCTTCTGGATCAGACTGTTGTTGGTTATCTGGTGTGGAGTAAGTGCA  
CTTAGCATGCTGACTTGCTCATCAGTTTTTGCACAGTGGCAATTTTGGGACTGATTTAGAACAG  
AAACTCCATTGGAACCCCGAGGACAAAGGTTATGTGCTTCACATGATCACTACTGCAGCAGAA  
TGGTCTATGTCATTTTTCCTTCTTTGGTTTTTTCCTGACTTACATTCGTGATTTTCAGAAAATT  
TCTTTACGGGTGGAAGCCAATTTACATGGATTAACCCTCTATGACACTGCACCTTGCCCTATT  
AACAATGAACGAACACGGCTACTTTCCAGAGATATTTGATGAAAGGATAAAATATTTCTGTAA  
TGATTATGATTCTCAGGGATTGGGGAAAGGTTACAGAAGTTGCTTATTCTTCTCTGAAATTT  
TCAACCACTTAATCAAGGCTGACAGTAACACTGATGAATGCTGATAATCAGGAAACATGAAAG  
AAGCCATTTGATAGATTATTCTAAAGGATATCATCAAGAAGACTATTAAAAACACCTATGCCT  
ATACTTTTTTATCTCAGAAAATAAAGTCAAAAGACTATG

3/168

**FIGURE 3**

CGGACGCGTGGGCGGACGCGTGGGGGAGAGCCGCGAGTCCCGGCTGCAGCACCTGGGAGAAGGC  
AGACCGTGTGAGGGGGCCTGTGGCCCCAGCGTGCTGTGGCCTCGGGGAGTGGGAAGTGGAGGC  
AGGAGCCTTCCTTACACTTCGCCATGAGTTTCCTCATCGACTCCAGCATCATGATTACCTCCC  
AGATACTATTTTTTGGATTTGGGTGGCTTTTCTTCATGCGCCAATTGTTTAAAGACTATGAGA  
TACGTCAGTATGTTGTACAGGTGATCTTCTCCGTGACGTTTGCATTTTCTTGCACCATGTTTG  
AGCTCATCATCTTTGAAATCTTAGGAGTATTGAATAGCAGCTCCCGTTATTTTCACTGGAAAA  
TGAACCTGTGTGTAATTCTGCTGATCCTGGTTTTTCATGGTGCCTTTTTTACATTGGCTATTTTA  
TTGTGAGCAATATCCGACTACTGCATAAACAACGACTGCTTTTTTCTGTCTCTTATGGCTGA  
CCTTTATGTATTTCTTCTGGAACTAGGAGATCCCTTTCCCATTCCTCAGCCCCAAAACATGGGA  
TCTTATCCATAGAACAGCTCATCAGCCGGGTGGTGTGATTGGAGTGACTCTCATGGCTCTTC  
TTTCTGGATTTGGTGTGTCAACTGCCCATACACTTACATGTCTTACTTCCTCAGGAATGTGA  
CTGACACGGATATTCTAGCCCTGGAACGGCGACTGCTGCAAACCATGGATATGATCATAAGCA  
AAAAGAAAAGGATGGCAATGGCACGGAGAACAATGTTCCAGAAGGGGGAAGTGCATAACAAAC  
CATCAGGTTTCTGGGGAATGATAAAAAGTGTTACCACTTCAGCATCAGGAAGTGAAAATCTTA  
CTCTTATTCAACAGGAAGTGGATGCTTTGGAAGAATTAAGCAGGCAGCTTTTTTCTGGAAACAG  
CTGATCTATATGCTACCAAGGAGAGAATAGAATACTCCAAAACCTTCAAGGGGAAATATTTTA  
ATTTTCTTGGTTACTTTTTCTCTATTTACTGTGTTTGGAAAATTTTCATGGCTACCATCAATA  
TTGTTTTTGATCGAGTTGGGAAAACGGATCCTGTCACAAGAGGCATTGAGATCACTGTGAATT  
ATCTGGGAATCCAATTTGATGTGAAGTTTTGGTCCCAACACATTTCTTCATTCTTGTGGAA  
TAATCATCGTCACATCCATCAGAGGATTGCTGATCACTCTTACCAAGTTCTTTTATGCCATCT  
CTAGCAGTAAGTCCTCCAATGTCATTGTCCTGCTATTAGCACAGATAATGGGCATGTACTTTG  
TCTCCTCTGTGCTGCTGATCCGAATGAGTATGCCTTTAGAATACCGCACCATAATCACTGAAG  
TCCTTGGAGAACTGCAGTTCAACTTCTATCACCGTTGGTTTGATGTGATCTTCCTGGTCAGCG  
CTCTCTCTAGCATACTCTTCCTCTATTTGGCTCACAAACAGGCACCAGAGAAGCAAATGGCAC  
CTTGAACTTAAGCCTACTACAGACTGTTAGAGGCCAGTGTTTCAAATTTAGATATAAGAGG  
GGGGAAAATGGAACCAGGGCCTGACATTTTATAAACAAACAAAATGCTATGGTAGCATTTTTT  
CACCTTCATAGCATACTCCTTCCCCGTCAGGTGATACTATGACCATGAGTAGCATCAGCCAGA  
ACATGAGAGGGGAGAACTAACTCAAGACAATACTCAGCAGAGAGCATCCCGTGTGGATATGAGG  
CTGGTGTAGAGGCGGAGAGGAGCCAAGAACTAAAGGTGAAAAATACACTGGAACCTCTGGGGC  
AAGACATGTCTATGGTAGCTGAGCCAAACACGTAGGATTTCCGTTTTAAGGTTACATGGAAA  
AGGTTATAGCTTTGCCTTGAGATTGACTCATTAATAATCAGAGACTGTAACAAAAAAAAAAAAA  
AAAAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGAAGCTTGGCCGCCATGGCCCAACT  
TGTTTATTGCAGCTTATAATG

5/168

**FIGURE 5**

AGCAGGGAAATCCGGATGTCTCGGTTATGAAGTGGAGCAGTGAGTGTGAGCCTCAACATAGTT  
CCAGA ACTCTCCATCCGGACTAGTTATTGAGCATCTGCCTCTCATATCACCAGTGGCCATCTG  
AGGTGTTTCCCTGGCTCTGAAGGGGTAGGCACGATGGCCAGGTGCTTCAGCCTGGTGTTGCTT  
CTCACTTCCATCTGGACCACGAGGCTCCTGGTCCAAGGCTCTTTGCGTGCAGAAGAGCTTTCC  
ATCCAGGTGTCATGCAGAATTATGGGGATCACCTTGTGAGCAAAAAGGCGAACCAGCAGCTG  
AATTTACAGAAGCTAAGGAGGCCTGTAGGCTGCTGGGACTAAGTTTGGCCGGCAAGGACCAA  
GTTGAAACAGCCTTGAAAGCTAGCTTTGAAACTTGCAGCTATGGCTGGGTTGGAGATGGATT  
GTGGTCATCTCTAGGATTAGCCCAAACCCCAAGTGTGGGAAAAATGGGGTGGGTGTCCTGATT  
TGGAAGGTTCCAGTGAGCCGACAGTTTGCAGCCTATTGTTACAACCTCATCTGATACTTGGACT  
AACTCGTGCATTCCAGAAATTATCACCACCAAAGATCCCATATTCAACACTCAAACCTGCAACA  
CAAACAACAGAATTTATTGTCAGTGACAGTACCTACTCGGTGGCATCCCCTTACTCTACAATA  
CCTGCCCCCTACTACTCCTCCTGCTCCAGCTTCCACTTCTATTCCACGGAGAAAAAATTG  
ATTTGTGTCACAGAAGTTTTTATGGAACTAGCACCATGTCTACAGAACTGAACCATTTGTT  
GAAAATAAAGCAGCATTCAAGAATGAAGCTGCTGGGTTTGGAGGTGTCCCCACGGCTCTGCTA  
GTGCTTGCTCTCCTCTTCTTTGGTGCTGCAGCTGGTCTTGGATTTTGCTATGTCAAAGGTAT  
GTGAAGGCCTTCCCTTTTACAAACAAGAATCAGCAGAAGGAAATGATCGAAACCAAAGTAGTA  
AAGGAGGAGAAGGCCAATGATAGCAACCCTAATGAGGAATCAAAGAAAACCTGATAAAAACCA  
GAAGAGTCCAAGAGTCCAAGCAAACTACCGTGCGATGCCTGGAAGCTGAAGTTTAGATGAGA  
CAGAAATGAGGAGACACACCTGAGGCTGGTTTTCTTTTCATGCTCCTTACCCTGCCCCAGCTGGG  
GAAATCAAAGGGGCCAAAGAACCAAAGAAGAAAGTCCACCCTTGGTTCCTAACTGGAATCAGC  
TCAGGACTGCCATTGGACTATGGAGTGCACCAAAGAGAATGCCCTTCTCCTTATTGTAACCCT  
GTCTGGATCCTATCCTCCTACCTCCAAAGCTTCCCACGGCCTTTCTAGCCTGGCTATGTCTTA  
ATAATATCCCCTGAGGAGAAAGGAGTTTTTGCAAAGTGCAAGGACCTAAAACATCTCATCAGTA  
TCCAGTGGTAAAAAGGCCTCCTGGCTGTCTGAGGCTAGGTGGGTTGAAAGCCAAGGAGTCACT  
GAGACCAAGGCTTTCTCTACTGATTCCGCAGCTCAGACCCTTTCTTCAGCTCTGAAAGAGAAA  
CACGTATCCCACCTGACATGTCCTTCTGAGCCCGGTAAGAGCAAAAGAATGGCAGAAAAGTTT  
AGCCCCTGAAAGCCATGGAGATTCTCATAACTTGAGACCTAATCTCTGTAAAGCTAAAATAAA  
GAAATAGAACAAGGCTGAGGATACGACAGTACACTGTCAGCAGGGACTGTAAACACAGACAGG  
GTCAAAGTGTTTTCTCTGAACACATTGAGTTGGAATCACTGTTTAGAACACACACACTTACTT  
TTTCTGGTCTCTACCACTGCTGATATTTTCTCTAGGAAATATACTTTTACAAGTAACAAAAAT  
AAAACTCTTATAAATTTCTATTTTTATCTGAGTTACAGAAATGATTACTAAGGAAGATTACT  
CAGTAATTTGTTTAAAAAGTAATAAAATTCAACAAACATTTGCTGAATAGCTACTATATGTCA  
AGTGCTGTGCAAGGTATTACACTCTGTAATTGAATATTATTCTCTCAAAAAATTGCACATAGTA  
GAACGCTATCTGGGAAGCTATTTTTTTTTCAGTTTTGATATTTCTAGCTTATCTACTTCCAACT  
AATTTTTATTTTTGCTGAGACTAATCTTATTCATTTTCTCTAATATGGCAACCATTATAACCT  
TAATTTATTATTAAACATACCTAAGAAGTACATTGTTACCTCTATATACCAAAGCACATTTTAA  
AAGTGCCATTAAACAAATGTATCACTAGCCCTCCTTTTTTCCAACAAGAAGGGACTGAGAGATGC  
AGAAATATTTGTGACAAAAAATTAAAGCATTTAGAAAACTT

7/168

**FIGURE 7**

CGCCGCGCTCCCGCACCCGCGGCCCGCCACCGCGCCGCTCCCGCATCTGCACCCGCGAGCCCG  
GCGGCCTCCCGGCGGGAGCGAGCAGATCCAGTCCGGCCCCGCGAGCGCAACTCGGTCCAGTCGGG  
GCGGCGGCTGCGGGCGCAGAGCGGAGATGAGCGGGCTTGGGGCCACCCTGCTGTGCCTGCTGC  
TGGCGGCGGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCGACCTCGGCTCCAGTCAAGC  
CCGGCCCCGGCTCTCAGCTACCCGCGAGGAGGAGGCCACCCTCAATGAGATGTTCCGCGAGGTTG  
AGGAACTGATGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGGAAGAGATGGAGGCAGAAG  
AAGCTGCTGCTAAAGCATCATCAGAAGTGAACCTGGCAAACCTTACCTCCCAGCTATCACAATG  
AGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCACCGAGAAATTCACAAGA  
TAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAGTTATCACATCTGTGGGAGACG  
AAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACGAGGACTGTGGGGCCAGCATGTACTGCC  
AGTTTGCCAGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTCTGCACCCGGG  
ACAGTGAGTGCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGG  
GCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCC  
AGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACC  
CCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGAT  
GCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGC  
CGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCCGATG  
AGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGGAGCC  
TGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGAGGGGAAG  
AGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCCA  
GGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCCTACATCTTCTTCCCAGTAAGTTTCC  
CCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTTCAGCTCCCCCAGGCTGTTTCTCCAGGC  
TTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACCCCT  
GTCCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTCTACATGGCTT  
TGATAATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTTGGGG  
AAATGTGGAGAAGAGTGCCCTGCTTTGCAACATCAACCTGGCAAAAATGCAACAAATGAATT  
TTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGT  
TCTGTTACCCCTGCATTACATGTGTTTATTTCATCCAGCAGTGTGCTCAGCTCCTACCTCTGT  
GCCAGGGCAGCATTTTTCATATCCAAGATCAATTCCTCTCTCAGCACAGCCTGGGGAGGGGGT  
CATTGTTCTCCTCGTCCATCAGGGATCTCAGAGGCTCAGAGACTGCAAGCTGCTTGCCCAAGT  
CACACAGCTAGTGAAGACCAGAGCAGTTTTCATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTC  
CACTACCCACACCAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATT  
TTTCTTGAGGCATGCACATCTGGAATTAAGGTCAAACCTAATTCTCACATCCCTCTAAAAGTAA  
ACTACTGTTAGGAACAGCAGTGTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAAT  
GATATTGACACTGTCCCTCTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCG  
TAGCATAACAGGTTAACCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGA  
AATTTGCAAAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACC  
GAGCAGGGCTGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTC  
CACAAATGATGTTTTTCAGGTGTGATGGACTGTTGCCACCATGTATTTCATCCAGAGTTCTTAAA  
GTTTTAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACAT  
AAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCAAAAAAAAAAAAAAAAAAAAAA  
AAA

9/168

**FIGURE 9**

CGGACGCGTGGGCGGACGCGTGGGGGCTGTGAGAAAGTGCCAATAAATACATCATGCAACCCC  
ACGGCCCACCTTGTGAACTCCTCGTGCCAGGGCTGATGTGCGTCTTCCAGGGCTACTCATCC  
AAAGGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCCTGGGGCTCTTCTGG  
ACCCTTAACTGGGTACTGGCCCTGGGCCAATGCGTCCTCGCTGGAGCCTTTGCCTCCTTCTAC  
TGGGCCTTCCACAAGCCCCAGGACATCCCTACCTTCCCCCTTAATCTCTGCCTTCATCCGCACA  
CTCCGTTACCACACTGGGTCAATTGGCATTGAGAGCCCTCATCCTGACCCTTGTGCAGATAGCC  
CGGGTCATCTTGGAGTATATTGACCACAAGCTCAGAGGAGTGCAGAACCTGTAGCCCGCTGC  
ATCATGTGCTGTTTCAAGTGCTGCCTCTGGTGTCTGGAAAAATTTATCAAGTTCCTAAACCGC  
AATGCATACATCATGATCGCCATCTACGGGAAGAATTTCTGTGTCTCAGCCAAAAATGCGTTC  
ATGCTACTCATGCGAAACATTGTCAGGGTGGTCGTCCTGGACAAAGTCACAGACCTGCTGCTG  
TTCTTTGGGAAGCTGCTGGTGGTTCGGAGGCGTGGGGGTCCTGTCCTTCTTTTTTTTCTCCGGT  
CGCATCCCGGGGCTGGGTAAAGACTTTAAGAGCCCCACCTCAACTATTACTGGCTGCCCATC  
ATGACCTCCATCCTGGGGGCCTATGTCATCGCCAGCGGCTTCTTCAGCGTTTTTCGGCATGTGT  
GTGGACACGCTCTTCCTCTGCTTCCTGGAAGACCTGGAGCGGAACAACGGCTCCCTGGACCGG  
CCCTACTACATGTCCAAGAGCCTTCTAAAGATTCTGGGCAAGAAGAACGAGGCGCCCCCGGAC  
AACAAGAAGAGGAAGAAGTGACAGCTCCGGCCCTGATCCAGGACTGCACCCCACCCCCACCGT  
CCAGCCATCCAACCTCACTTCGCCTTACAGGTCTCCATTTTGTGGTAAAAAAAGGTTTTAGGC  
CAGGCGCCGTGGCTCACGCCTGTAATCCAACACTTTGAGAGGCTGAGGCGGGCGGATCACCTG  
AGTCAGGAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTCCGTCTCTATTAAAAATACAA  
AAATTAGCCGAGAGTGGTGGCATGCACCTGTCATCCCAGCTACTCGGGAGGCTGAGGCAGGAG  
AATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCGAGATCGCGCCACTGCACTCCAACC  
TGGGTGACAGACTCTGTCTCCAAAACAAAACAAACAAACAAAAGATTTTATTAAAGATATTT  
TGTAACTC



11/168

**FIGURE 11**

GCCCCGCGCCCGGCGCCGGGCGCCCCGAAGCCGGGAGCCACCGCCATGGGGGCCTGCCTGGGAG  
CCTGCTCCCTGCTCAGCTGCGCGTCCTGCCTCTGCGGCTCTGCCCCCTGCATCCTGTGCAGCT  
GCTGCCCCGCCAGCCGCAACTCCACCGTGAGCCGCCTCATCTTCACGTTCTTCCTCTTCCTGG  
GGGTGCTGGTGTCCATCATTATGCTGAGCCCGGGCGTGAGAGTCAGCTCTACAAGCTGCCCT  
GGGTGTGTGAGGAGGGGGCCGGGATCCCCACCGTCCTGCAGGGCCACATCGACTGTGGCTCCC  
TGCTTGGCTACCGCGCTGTCTACCGCATGTGCTTCGCCACGGCGGCCTTCTTCTTCTTCTTTT  
TCACCCTGCTCATGCTCTGCGTGAGCAGCAGCCGGGACCCCCGGGCTGCCATCCAGAATGGGT  
TTTGGTTCTTTAAGTTCCTGATCCTGGTGGGCCTCACCGTGGGTGCCTTCTACATCCCTGACG  
GCTCCTTCACCAACATCTGGTTCTACTTCGGCGTCGTGGGCTCCTTCCTCTTCATCCTCATCC  
AGCTGGTGCTGCTCATCGACTTTGCGCACTCCTGGAACCAGCGGTGGCTGGGCAAGGCCGAGG  
AGTGCGATTCCCGTGCCCTGGTACGCAGGCCTCTTCTTCTTCACTCTCCTCTTCTACTTGCTGT  
CGATCGCGGCCGTGGCGCTGATGTTTCATGTACTACACTGAGCCCAGCGGCTGCCACGAGGGCA  
AGGTCTTCATCAGCCTCAACCTCACCTTCTGTGTCTGCGTGTCATCGCTGCTGTCCTGCCCA  
AGGTCCAGGACGCCCAGCCCAACTCGGGTCTGCTGCAGGCCTCGGTTCATCACCCCTCTACACCA  
TGTTTGTACCTGGTCAGCCCTATCCAGTATCCCTGAACAGAAATGCAACCCCCATTTGCCAA  
CCCAGCTGGGCAACGAGACAGTTGTGGCAGGCCCCGAGGGCTATGAGACCCAGTGGTGGGATG  
CCCCGAGCATTGTGGGCCTCATCATCTTCCTCCTGTGCACCCTCTTCATCAGTCTGCGCTCCT  
CAGACCACCGGCAGGTGAACAGCCTGATGCAGACCGAGGAGTGCCACCTATGCTAGACGCCA  
CACAGCAGCAGCAGCAGCAGGTGGCAGCCTGTGAGGGCCGGGCCTTTGACAACGAGCAGGACG  
GCGTCACCTACAGCTACTCCTTCTTCCACTTCTGCCTGGTGCTGGCCTCACTGCACGTCATGA  
TGACGCTCACCAACTGGTACAAGCCCGGTGAGACCCGGAAGATGATCAGCACGTGGACCGCCG  
TGTGGGTGAAGATCTGTGCCAGCTGGGCAGGGCTGCTCCTCTACCTGTGGACCCTGGTAGCCC  
CACTCCTCCTGCGCAACCGCGACTTCAGCTGAGGCAGCCTCACAGCCTGCCATCTGGTGCCTC  
CTGCCACCTGGTGCCTCTCGGCTCGGTGACAGCCAACCTGCCCCCTCCCCACACCAATCAGCC  
AGGCTGAGCCCCCACCCTGCCCCAGCTCCAGGACCTGCCCCTGAGCCGGGCCTTCTAGTCGT  
AGTGCCCTTCAGGGTCCGAGGAGCATCAGGCTCCTGCAGAGCCCCATCCCCCGCCACACCCAC  
ACGGTGGAGCTGCCTCTTCCTTCCCCCTCCTCCTGTTGCCATACTCAGCATCTCGGATGAAA  
GGGCTCCCTTGTCTCAGGCTCCACGGGAGCGGGGCTGCTGGAGAGAGCGGGGAACTCCCACC  
ACAGTGGGGCATCCGGCACTGAAGCCCTGGTGTTCCTGGTCACGTCCCCCAGGGGACCCTGCC  
CCCTTCTGACTTCGTGCCTTACTGAGTCTCTAAGACTTTTTCTAATAAACAAGCCAGTGCG  
TGTAATAAAAAA

13/168

**FIGURE 13**

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCACCCGTTAAGGTGTCTTCTCTTTAGGGATGGT  
GAGGTTGGAAAAAGACTCCTGTAACCCTCCTCCAGGATGAACCACCTGCCAGAAGACATGGAG  
AACGCTCTCACCGGGAGCCAGAGCTCCCATGCTTCTCTGCGCAATATCCATTCATCAACCCC  
ACACAACCTCATGGCCAGGATTGAGTCCTATGAAGGAAGGGAAAAGAAAGGCATATCTGATGTC  
AGGAGGACTTTCTGTTTGTGTTGTCACCTTTGACCTCTTATTCGTAACATTACTGTGGATAATA  
GAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGAGGTGATGCAGTATGACTAC  
TATTCTTCATATTTTGATATATTTCTTCTGGCAGTTTTTCGATTTAAAGTGTTAATACTTGCA  
TATGCTGTGTGCAGACTGCGCCATTGGTGGGCAATAGCGTTGACAACGGCAGTGACCAGTGCC  
TTTTTACTAGCAAAAGTGATCCTTTTGAAGCTTTTCTCTCAAGGGGCTTTTGGCTATGTGCTG  
CCCATCATTTTCATTCATCCTTGCCTGGATTGAGACGTGGTTCCTGGATTTCAAAGTGTTACCT  
CAAGAAGCAGAAGAAGAAAACAGACTCCTGATAGTTCAGGATGCTTCAGAGAGGGCAGCACTT  
ATACCTGGTGGTCTTTCTGATGGTCAGTTTTATTCCCCTCCTGAATCCGAAGCAGGATCTGAA  
GAAGCTGAAGAAAAACAGGACAGTGAGAAACCACTTTTAGAACTATGAGTACTACTTTTGTTA  
AATGTGAAAAACCCTCACAGAAAGTCATCGAGGCAAAAAGAGGCAGGCAGTGGAGTCTCCCTG  
TCGACAGTAAAGTTGAAATGGTGACGTCCACTGCTGGCTTTATTGAACAGCTAATAAAGATTT  
ATTTATTGTAATACCTCACAAACGTTGTACCATATCCATGCACATTTAGTTGCCTGCCTGTGG  
CTGGTAAGGTAATGTCATGATTCATCCTCTCTTCAGTGAGACTGAGCCTGATGTGTAAACAAA  
TAGGTGAAGAAAGTCTTGCTGTATTCCCTAATCAAAAGACTTAATATATTGAAGTAACACTT  
TTTTAGTAAGCAAGATACCTTTTTATTTCAATTCACAGAATGGAATTTTTTTGTTTCATGTCT  
CAGATTTATTTTGATTTCTTTTTTAACACTCTACATTTCCCTTGTTTTTTAACTCATGCACA  
TGTGCTCTTTGTACAGTTTTAAAAAGTGTAATAAAATCTGACATGTCAATGTGGCTAGTTTTA  
TTTTTCTTGTTTTGCATTATGTGTATGGCCTGAAGTGTTGGACTTGCAAAAGGGGAAGAAAGG  
AATTGCGAATACATGTAAAATGTCACCAGACATTTGTATTATTTTTATCATGAAATCATGTTT  
TTCTCTGATTGTTCTGAAATGTTCTAAATACTCTTATTTTGAATGCACAAAATGACTTAAACC  
ATTCATATCATGTTTCCTTTGCGTTCAGCCAATTTCAATTAAAATGAACTAAATTAATAA

15/168

**FIGURE 15**

ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCCTCGGGCCCCGACCCGCCAGGAAAGACTGA  
GGCCGCGGCCTGCCCCGCCCCGGCTCCCTGCGCCGCCGCCGCTCCCGGGACAGAAG**ATGT**GCT  
CCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGGTGCAGGGCT  
GCCCATCCGGCTGCCAGTGCCAGCCAGCCACAGACAGTCTTCTGCACTGCCCCGCCAGGGGACCA  
CGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTGAGAACGGCATCACCA  
TGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCCTGGACCTGTCACAGAACC  
AGATCGCCAGCCTGCCAGCGGGGTCTTCCAGCCACTCGCCAACCTCAGCAACCTGGACCTGA  
CGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCCGTGGCCTGCGGCGCCTCGAGCGCC  
TCTACCTGGGCAAGAACCGCATCCGCCACATCCAGCCTGGTGCCTTCGACACGCTCGACCGCC  
TCCTGGAGCTCAAGCTGCAGGACAACGAGCTGCGGGCACTGCCCCCGCTGCGCCTGCCCCGCC  
TGCTGCTGCTGGACCTCAGCCACAACAGCCTCCTGGCCCTGGAGCCCGGCATCCTGGACACTG  
CCAACGTGGAGGCGCTGCGGCTGGCTGGTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCA  
GCCGCTTGCGCAACCTCCACGACCTGGATGTGTCCGACAACCAGCTGGAGCGAGTGCCACCTG  
TGATCCGAGGCCTCCGGGGCCTGACGCGCCTGCGGCTGGCCGGCAACACCCGCATTGCCCAGC  
TGCGGCCCCGAGGACCTGGCCGGCCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCC  
TGCAGGCCCTGCCTGGCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCCC  
GCAACCCCTTCAACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCCTGGGTGCGCGAGAGCCACG  
TCACACTGGCCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCCAAGAACGCTGGCCGGCTGC  
TCCTGGAGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACACAGCCACAGTGCCCA  
CCACGAGGCCCCGTGGTGCAGGAGCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTA  
GCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCCGCCCTCCACTGCCCCACCGACTGTAGGGC  
CTGTCCCCCAGCCCCAGGACTGCCCACCCTCCACCTGCCTCAATGGGGGCACATGCCACCTGG  
GGACACGGCACCCACCTGGCGTGCTTGTGCCCCGAAGGCTTACGGGCCTGTACTGTGAGAGCC  
AGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCACGCCGAGGGCCACCACGGTCCCTGA  
CCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGCAGCGCTACCTCCAGG  
GGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACCTATCGGGCCCTGATAAGC  
GGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTGAGTACACGGTCACCCAGCTGCGGGCCCA  
ACGCCACTTACTCCGTCTGTGTATGCCTTTGGGGCCCCGGGCGGGTGCCGGAGGGGCGAGGAGG  
CCTGCGGGGAGGGCCATACACCCCCAGCCGTCCACTCCAACCACGCCCCAGTCACCCAGGCCC  
GCGAGGGCAACCTGCCGCTCCTCATTGCGCCCGCCCTGGCCGCGGTGCTCCTGGCCGCGCTGG  
CTGCGGTGGGGGCAGCCTACTGTGTGCGGCGGGGGCGGGCCATGGCAGCAGCGGCTCAGGACA  
AAGGGCAGGTGGGGCCAGGGGCTGGGCCCCCTGGAAGTGGAGGGAGTGAAGGTCCCTTGGAGC  
CAGGCCCCGAAGGCAACAGAGGGCGGTGGAGAGGCCCTGCCAGCGGGTCTGAGTGTGAGGTGC  
CACTCATGGGCTTCCCAGGGCCTGGCCTCCAGTCACCCCTCCACGCAAAGCCCTACATC**TAA**G  
CCAGAGAGAGACAGGGCAGCTGGGGCCGGGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTG  
CTGCCACACCACGTAAGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGAC  
CACAGCTGGGCCCTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGC  
TGACGAGCCCTAACGTCCCCAGAACCGAGTGCCATATGAGGACAGTGTCCGCCCTGCCCTCCGC  
AACGTGCAGTCCCTGGGCACGGCGGGCCCTGCCATGTGCTGGTAACGCATGCCTGGGTCTGC  
TGGGCTCTCCCACTCCAGGCGGACCCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAG  
GGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAAGAA  
ACTGGAAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAAATATATATATTTATAAGAG  
ATCCTTTCCCATTTATTCTGGGAAGATGTTTTTCAAACCTCAGAGACAAGGACTTTGGTTTTTG  
TAAGACAAACGATGATATGAAGGCCTTTTGTAAGAAAAAATAAAAGATGAAGTGTGAAA

17/168

**FIGURE 17**

GCAGCGGCGAGGCGGCGGTGGTGGCTGAGTCCGTGGTGGCAGAGGCGAAGGCGACAGCTCATG  
CGGGTCCGGATAGGGCTGACGCTGCTGCTGTGTGCGGTGCTGCTGAGCTTGGCCTCGGCGTCC  
TCGGATGAAGAAGGCAGCCAGGATGAATCCTTAGATTCCAAGACTACTTTGACATCAGATGAG  
TCAGTAAAGGACCATACTACTGCAGGCAGAGTAGTTGCTGGTCAAATATTTCTTGATTCAGAA  
GAATCTGAATTAGAATCCTCTATTCAAGAAGAGGAAGACAGCCTCAAGAGCCAAGAGGGGGAA  
AGTGTACAGAAAGATATCAGCTTTCTAGAGTCTCCAAATCCAGAAAACAAGGACTATGAAGAG  
CCAAAGAAAGTACGGAAACCAGCTTTGACCGCCATTGAAGGCACAGCACATGGGGAGCCCTGC  
CACTTCCCTTTTCTTTTCCTAGATAAGGAGTATGATGAATGTACATCAGATGGGAGGGAAGAT  
GGCAGACTGTGGTGTGCTACAACCTATGACTACAAAGCAGATGAAAAGTGGGGCTTTTGTGAA  
ACTGAAGAAGAGGCTGCTAAGAGACGGCAGATGCAGGAAGCAGAAATGATGTATCAAACCTGGA  
ATGAAAATCCTTAATGGAAGCAATAAGAAAAGCCAAAAAAGAGAAGCATATCGGTATCTCCAA  
AAGGCAGCAAGCATGAACCATAACAAAGCCCTGGAGAGAGTGTATATGCTCTTTTATTTGGT  
GATTACTTGCCACAGAATATCCAGGCAGCGAGAGAGATGTTTGAGAAGCTGACTGAGGAAGGC  
TCTCCCAAGGGACAGACTGCTCTTGGCTTTCTGTATGCCTCTGGACTTGGTGTTAATTCAAGT  
CAGGCAAAGGCTCTTGTATATTATACATTTGGAGCTCTTGGGGGCAATCTAATAGCCCACATG  
GTTTTGGTAAGTAGACTTTAGTGGAAGGCTAATAATATTAACATCAGAAGAATTTGTGGTTTA  
TAGCGGCCACAACCTTTTTTCAGCTTTCATGATCCAGATTTGCTTGTATTAAGACCAAATATTCA  
GTTGAACCTTCCTTCAAATTCTTGTTAATGGATATAACACATGGAATCTACATGTAAATGAAAG  
TTGGTGGAGTCCACAATTTTTCTTTAAAATGATTAGTTTGGCTGATTGCCCCTAAAAAGAGAG  
ATCTGATAAATGGCTCTTTTTTAAATTTTCTCTGAGTTGGAATTGTCAGAATCATTTTTTACAT  
TAGATTATCATAATTTTTAAAAATTTTCTTTAGTTTTTCAAATTTTGTAAATGGTGGCTATA  
GAAAAACAACATGAAATATTATACAATATTTTGCAACAATGCCCTAAGAATTGTAAAATTCA  
TGGAGTTATTTGTGCAGAATGACTCCAGAGAGCTCTACTTTCTGTTTTTTTACTTTTCATGATT  
GGCTGTCTTCCCATTATTCTGGTCATTTATTGCTAGTGACACTGTGCCTGCTTCCAGTAGTC  
TCATTTTCCCTATTTTGCTAATTTGTTACTTTTTCTTTGCTAATTTGGAAGATTAACTCATTT  
TTAATAAAATTATGTCTAAGATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

19/168

**FIGURE 19**

AATTCAGATTTTAAAGCCCATTCTGCAGTGGAATTCATGAACTAGCAAGAGGACACCATCTTC  
TTGTATTATACAAGAAAGGAGTGTAACCTATCACACACAGGGGGGAAAAATGCTCTTTTGGGTGC  
TAGGCCTCCTAATCCTCTGTGGTTTTCTGTGGACTCGTAAAGGAAACTAAAGATTGAAGACA  
TCACTGATAAGTACATTTTTATCACTGGATGTGACTCGGGCTTTGGAAACTTGGCAGCCAGAA  
CTTTTGATAAAAAGGGATTTTCATGTAATCGCTGCCTGTCTGACTGAATCAGGATCAACAGCTT  
TAAAGGCAGAAACCTCAGAGAGACTTCGTACTGTGCTTCTGGATGTGACCGACCCAGAGAATG  
TCAAGAGGACTGCCCAGTGGGTGAAGAACCAAGTTGGGGAGAAAGGTCTCTGGGGTCTGATCA  
ATAATGCTGGTGTTCCTGGCGTGCTGGCTCCCCTGACTGGCTGACACTAGAGGACTACAGAG  
AACCTATTGAAGTGAACCTGTTTGGACTCATCAGTGTGACACTAAATATGCTTCCTTTGGTCA  
AGAAAGCTCAAGGGAGAGTTATTAATGTCTCCAGTGTTGGAGGTCGCCTTGCAATCGTTGGAG  
GGGGCTATACTCCATCCAAATATGCAGTGGAAGGTTTCAATGACAGCTTAAGACGGGACATGA  
AAGCTTTTGGTGTGCACGTCTCATGCATTGAACCAGGATTGTTCAAACAAACTTGGCAGATC  
CAGTAAAGGTAATTGAAAAAAACTCGCCATTTGGGAGCAGCTGTCTCCAGACATCAAACAAC  
AATATGGAGAAGGTTACATTGAAAAAGTCTAGACAAACTGAAAGGCAATAAATCCTATGTGA  
ACATGGACCTCTCTCCGGTGGTAGAGTGCATGGACCACGCTCTAACAAGTCTCTTCCCTAAGA  
CTCATTATGCCGCTGGAAAAGATGCCAAAATTTTCTGGATACCTCTGTCTCACATGCCAGCAG  
CTTTGCAAGACTTTTTATTGTTGAAACAGAAAGCAGAGCTGGCTAATCCCAAGGCAGTGTTGAC  
TCAGCTAACCACAAATGTCTCCTCCAGGCTATGAAATTGGCCGATTTCAAGAACACATCTCCT  
TTTCAACCCCATTCCTTATCTGCTCCAACCTGGACTCATTTAGATCGTGCTTATTTGGATTGC  
AAAAGGGAGTCCCACCATCGCTGGTGGTATCCCAGGGTCCCTGCTCAAGTTTTCTTTGAAAAG  
GAGGGCTGGAATGGTACATCACATAGGCAAGTCTGCCCTGTATTTAGGCTTTGCCTGCTTGG  
TGTGATGTAAGGGAAATTGAAAGACTTGCCCATTCAAAATGATCTTTACCGTGGCCTGCCCCA  
TGCTTATGGTCCCCAGCATTTACAGTAACTTGTGAATGTTAAGTATCATCTCTTATCTAAATA  
TTAAAAGATAAGTCAACCCAAAAA

21/168

**FIGURE 21**

CTGAGGCGGCGGTAGCATGGAGGGGGAGAGTACGTCGGCGGTGCTCTCGGGCTTTGTGCTCGG  
CGCACTCGCTTTCCAGCACCTCAACACGGACTCGGACACGGAAGGTTTTCTTCTTGGGGAAGT  
AAAAGGTGAAGCCAAGAACAGCATTACTGATTCCCAAATGGATGATGTTGAAGTTGTTTATAC  
AATTGACATTCAGAAATATATTCCATGCTATCAGCTTTTTAGCTTTTATAATTCTTCAGGCGA  
AGTAAATGAGCAAGCACTGAAGAAAATATTATCAAATGTCAAAAAGAATGTGGTAGGTTGGTA  
CAAATTCGGTCGTCATTCAGATCAGATCATGACGTTTAGAGAGAGGGCTGCTTCACAAAACCTT  
GCAGGAGCATTTTTCAAACCAAGACCTTGTTTTCTGCTATTAACACCAAGTATAATAACAGA  
AAGCTGCTCTACTCATCGACTGGAACATTCCTTATATAAACCTCAAAAAGGACTTTTTTCACAG  
GGTACCTTTAGTGGTTGCCAATCTGGGCATGTCTGAACAACTGGGTTATAAACTGTATCAGG  
TTCCTGTATGTCCACTGGTTTTAGCCGAGCAGTACAAACACACAGCTCTAAATTTTTTGAAGA  
AGATGGATCCTTAAAGGAGGTACATAAGATAAATGAAATGTATGCTTCATTACAAGAGGAATT  
AAAGAGTATATGCAAAAAAGTGGAAGACAGTGAACAAGCAGTAGATAAACTAGTAAAGGATGT  
AAACAGATTAAACGAGAAATTGAGAAAAGGAGAGGAGCACAGATTCAGGCAGCAAGAGAGAA  
GAACATCCAAAAAGACCCTCAGGAGAACATTTTTCTTTGTCAGGCATTACGGACCTTTTTTCC  
AAATTCTGAATTTCTTCATTCATGTGTTATGTCTTTAAAAAATAGACATGTTTCTAAAAGTAG  
CTGTA ACTACAACCACCATCTCGATGTAGTAGACAATCTGACCTTAATGGTAGAACACACTGA  
CATTCTGAAGCTAGTCCAGCTAGTACACCACAAATCATTAAGCATAAAGCCTTAGACTTAGA  
TGACAGATGGCAATTCAAGAGATCTCGGTTGTTAGATACACAAGACAAACGATCTAAAGCAA  
TACTGGTAGTAGTAACCAAGATAAAGCATCCAAATGAGCAGCCCAGAAACAGATGAAGAAAT  
TGAAAAGATGAAGGGTTTTGGTGAATATTCACGGTCTCCTACATTTTGATCCTTTTAACCTTA  
CAAGGAGATTTTTTTATTTGGCTGATGGGTAAAGCCAAACATTTCTATTGTTTTTACTATGTT  
GAGCTACTTGACAGTAAGTTCATTTGTTTTTACTATGTTACCTGTTTGCAGTAATACACAGAT  
AACTCTTAGTGCATTTACTTCACAAAGTACTTTTTCAAACATCAGATGCTTTTATTTCCAAAC  
CTTTTTTTCACCTTTCACTAAGTTGTTGAGGGGAAGGCTTACACAGACACATTCTTTAGAATT  
GGAAAAGTGAGACCAGGCACAGTGGCTCACACCTGTAATCCCAGCACTTAGGGAAGACAAGTC  
AGGAGGATTGATTGAAGCTAGGAGTTAGAGACCAGCCTGGGCAACGTATTGAGACCATGTCTA  
TTAAAAAATAAAATGGAAAAGCAAGAATAGCCTTATTTTCAAATATGGAAAGAAATTTATAT  
GAAAATTTATCTGAGTCATTAAAATTCTCCTTAAGTGATACTTTTTTAGAAGTACATTATGGC  
TAGAGTTGCCAGATAAAATGCTGGATATCATGCAATAAATTTGCAAAACATCATCTAAAATTT  
AAAAAAAAAAAAAAAAAAAAA

23/168

**FIGURE 23**

GGCACAGCCGCGCGGCGGAGGGCAGAGTCAGCCGAGCCGAGTCCAGCCGGACGAGCGGACCAGCGCAGGGCAGCC  
CAAGCAGCGCGCAGCGAACGCCCCGCCGCCGCCACACCCCTCTGCGGTCCCCGCGGCGCCTGCCACCCTTCCCTCC  
TTCCCCGCGTCCCCGCTCGCCGGCCAGTCAGCTTGCCGGGTTGCTGCCCCGCGAAACCCCGAGGTACCAGCC  
CGCGCCTCTGCTTCCCTGGGCCGCGCGCCGCTCCACGCCCTCCTTCTCCCTGGCCCCGGCGCCTGGCACCAGGGG  
ACCGTTGCCTGACGCGAGGCCCAGCTCTACTTTTCGCCCCGCGTCTCCTCCGCCTGCTCGCCTCTTCCACCAACT  
CCAACCTCCTTCTCCCTCCAGCTCCACTCGCTAGTCCCCGACTCCGCCAGCCCTCGGCCCCGCTGCCGTAGCGCCGC  
TTCCCGTCCGGTCCCAAAGGTGGGAACGCGTCCGCCCGGCCCGCACCATGGCAGGGTTTCGGCTTGCCCCGCGCTT  
CTCTGCACCCTGGCAGTGCTCAGCGCCGCGCTGCTGGCTGCCGAGCTCAAGTCGAAAAGTTGCTCGGAAGTGCGA  
CGTCTTTACGTGTCCAAAGGCTTCAACAAGAACGATGCCCCCTCCACGAGATCAACGGTGATCATTTGAAGATC  
TGTCCCCAGGGTTCTACCTGCTGCTCTCAAGAGATGGAGGAGAAGTACAGCCTGCAAAGTAAAGATGATTTCAA  
AGTGTGGTCAGCGAACAGTGCAATCATTTGCAAGCTGTCTTTGCTTCACGTTACAAGAAGTTTGATGAATTTCTTC  
AAAGAACTACTTGAAAATGCAGAGAAATCCCTGAATGATATGTTTGTGAAGACATATGGCCATTTATACATGCAA  
AATTCTGAGCTATTTAAAGATCTCTTCGTAGAGTTGAAACGTTACTACGTGGTGGGAAATGTGAACCTGGAAGAA  
ATGCTAAATGACTTCTGGGCTCGCCTCCTGGAGCGGATGTTCCGCCTGGTGAACCTCCAGTACCACCTTTACAGAT  
GAGTATCTGGAATGTGTGAGCAAGTATACGGAGCAGCTGAAGCCCTTCGGAGATGTCCCTCGCAAATTGAAGCTC  
CAGGTTACTCGTGCTTTTGTAGCAGCCCGTACTTTGCTCAAGGCTTAGCGGTTGCGGGAGATGTGCTGAGCAAG  
GTCTCCGTGGTAAACCCACAGCCAGTGTACCCATGCCCTGTTGAAGATGATCTACTGCTCCCACTGCCGGGGT  
CTCGTGACTGTGAAGCCATGTTACAACCTACTGCTCAAACATCATGAGAGGCTGTTTGGCCAACCAAGGGGATCTC  
GATTTTGAATGGAACAATTTATAGATGCTATGCTGATGGTGGCAGAGAGGCTAGAGGGTCTTTCAACATTGAA  
TCGGTCATGGATCCCATCGATGTGAAGATTTCTGATGCTATTATGAACATGCAGGATAATAGTGTTCAGTGTCT  
CAGAAGGTTTTCCAGGGATGTGGACCCCCAAGCCCTCCAGCTGGACGAATTTCTCGTTCATCTCTGAAAGT  
GCCTTCAGTGCTCGCTTCAGACCACATCACCCCGAGGAACGCCCAACCACAGCAGCTGGCACTAGTTTGGACCGA  
CTGGTTACTGATGTCAAGGAGAACTGAAACAGGCCAAGAAATCTGGTCTCCTTCCGAGCAACGTTTGAAC  
GATGAGAGGATGGCTGCAGGAAACGGCAATGAGGATGACTGTTGGAATGGGAAAGGCAAAAGCAGGTACCTGTTT  
GCAGTGACAGGAAATGGATTAGCCAACCAGGGCAACAACCCAGAGGTCCAGGTTGACACCAGCAAACCAGACATA  
CTGATCCTTCGTCAAATCATGGCTCTTCGAGTGATGACCAGCAAGATGAAGAATGCATACAATGGGAACGACGTG  
GACTTCTTTGATATCAGTGATGAAAGTAGTGGAGAAGGAAGTGGAAAGTGGCTGTGAGTATCAGCAGTGCCCTTCA  
GAGTTTGACTACAATGCCACTGACCATGCTGGGAAGAGTGCCAATGAGAAAGCCGACAGTGCTGGTGTCCGTCTC  
GGGGCACAGGCCTACCTCCTCACTGTCTTCTGCATCTTGTTTCTGGTTATGCAGAGAGAGTGGAGATTAATTCTCA  
AACTCTGAGAAAAAGTGTTTCATCAAAAAGTTAAAAGGCACCAGTTATCACTTTTCTACCATCCTAGTGACTTTGC  
TTTTTAAATGAATGGACAACAATGTACAGTTTTTACTATGTGGCCACTGGTTTAAGAAGTGCTGACTTTGTTTTC  
TCATTACAGTTTGGGAGGAAAAGGGACTGTGCATTGAGTTGGTTCCTGCTCCCCCAAACCATGTTAAACGTGGCT  
AACAGTGTAGGTACAGAACTATAGTTAGTTGTGCATTTGTGATTTTATCACTCTATTATTTGTTTGTATGTTTTT  
TTCTCATTTTCGTTTGTGGGTTTTTTTTTCCAACTGTGATCTCGCCTTGTTTCTTACAAGCAAACCAGGGTCCCTT  
CTTGGCACGTAACATGTACGTATTTCTGAAATATTAAATAGCTGTACAGAAGCAGGTTTTATTTATCATGTTATC  
TTATTAAAAGAAAAAGCCCCAAAAGC

25/168

**FIGURE 25**

CTCGCCCTCAAATGGGAACGCTGGCCTGGGACTAAAGCATAGACCACCAGGCTGAGTATCCTG  
ACCTGAGTCATCCCCAGGGATCAGGAGCCTCCAGCAGGGAACCTTCCATTATATTCTTCAAGC  
AACTTACAGCTGCACCGACAGTTGCGATGAAAGTTCTAATCTCTTCCCTCCTCCTGTTGCTGC  
CACTAATGCTGATGTCCATGGTCTCTAGCAGCCTGAATCCAGGGGTCGCCAGAGGCCACAGGG  
ACCGAGGCCAGGCTTCTAGGAGATGGCTCCAGGAAGGCGGCCAAGAATGTGAGTGCAAAGATT  
GGTTCCTGAGAGCCCCGAGAAGAAAATTTCATGACAGTGTCTGGGCTGCCAAAGAAGCAGTGCC  
CCTGTGATCATTTCAAGGGCAATGTGAAGAAAACAAGACACCAAAGGCACCACAGAAAGCCAA  
ACAAGCATTCCAGAGCCTGCCAGCAATTTCTCAAACAATGTCAGCTAAGAAGCTTTGCTCTGC  
CTTTGTAGGAGCTCTGAGCGCCCACTCTTCCAATTAAACATTCTCAGCCAAGAAGACAGTGAG  
CACACCTACCAGACACTCTTCTTCTCCACCTCACTCTCCCACTGTACCCACCCCTAAATCAT  
TCCAGTGCTCTCAAAAAGCATGTTTTTCAAGATCATTTTGTTTGTTGCTCTCTCTAGTGTCTT  
CTTCTCTCGTCAGTCTTAGCCTGTGCCCTCCCCTTACCCAGGCTTAGGCTTAATTACCTGAAA  
GATTCCAGGAACTGTAGCTTCCTAGCTAGTGTCATTTAACCTTAAATGCAATCAGGAAAGTA  
GCAAACAGAAGTCAATAAATATTTTAAATGTCAAAAAAAAAAAAAAAAAAAAA



27/168

**FIGURE 27**

GGACGCCAGCGCCTGCAGAGGCTGAGCAGGGAAAAAGCCAGTGCCCCAGCGGAAGCACAGCTC  
AGAGCTGGTCTGCCATGGACATCCTGGTCCCCTCCTGCAGCTGCTGGTGCTGCTTCTTACCC  
TGCCCCCTGCACCTCATGGCTCTGCTGGGCTGCTGGCAGCCCCCTGTGCAAAGCTACTTCCCCT  
ACCTGATGGCCGTGCTGACTCCCAAGAGCAACCGCAAGATGGAGAGCAAGAAACGGGAGCTCT  
TCAGCCAGATAAAGGGGCTTACAGGAGCCTCCGGGAAAGTGGCCCTACTGGAGCTGGGCTGCG  
GAACCGGAGCCAACTTTCAGTTCTACCCACCGGGCTGCAGGGTCACCTGCCTAGACCCAAATC  
CCCCTTTGAGAAGTTCCTGACAAAGAGCATGGCTGAGAACAGGCACCTCCAATATGAGCGGT  
TTGTGGTGGCTCCTGGAGAGGACATGAGACAGCTGGCTGATGGCTCCATGGATGTGGTGGTCT  
GCACTCTGGTGCTGTGCTCTGTGCAGAGCCCAAGGAAGGTCCTGCAGGAGGTCCGGAGAGTAC  
TGAGACCGGGAGGTGTGCTCTTTTTCTGGGAGCATGTGGCAGAACCATATGGAAGCTGGGCCT  
TCATGTGGCAGCAAGTTTTTCGAGCCCACCTGGAAACACATTGGGGATGGCTGCTGCCTCACCA  
GAGAGACCTGGAAGGATCTTGAGAACGCCAGTTCTCCGAAATCCAATGGAACGACAGCCCC  
CTCCCTTGAAGTGGCTACCTGTTGGGCCCCACATCATGGGAAAGGCTGTCAAACAATCTTTCC  
CAAGCTCCAAGGCACTCATTTGCTCCTTCCCCAGCCTCCAATTAGAACAAGCCACCCACCAGC  
CTATCTATCTTCCACTGAGAGGGACCTAGCAGAATGAGAGAAGACATTCTATGTACCACCTACT  
AGTCCCTCTCTCCCCAACCTCTGCCAGGGCAATCTCTAACTTCAATCCCGCCTTCGACAGTGA  
AAAAGCTCTACTTCTACGCTGACCCAGGGAGGAAACACTAGGACCCTGTTGTATCCTCAACTG  
CAAGTTTCTGGACTAGTCTCCAACGTTTGCCTCCCAATGTTGTCCCTTTCCTTCGTTCCCAT  
GGTAAAGCTCCTCTCGCTTTCCTCCTGAGGCTACACCCATGCGTCTCTAGGAACTGGTCACAA  
AAGTCATGGTGCCTGCATCCCTGCCAAGCCCCCTGACCCTCTCTCCCCACTACCACCTTCTT  
CCTGAGCTGGGGGCACCAGGGAGAATCAGAGATGCTGGGGATGCCAGAGCAAGACTCAAAGAG  
GCAGAGGTTTTGTTCTCAAATATTTTTTAATAAATAGACGAAACCACG

29/168

**FIGURE 29**

CAATGTTTGCCTATCCACCTCCCCCAAGCCCCTTTACCTATGCTGCTGCTAACGCTGCTGCTG  
CTGCTGCTGCTGCTTAAAGGCTCATGCTTGGAGTGGGGACTGGTCGGTGCCCAGAAAGTCTCT  
TCTGCCACTGACGCCCCCATCAGGGATTGGGCCTTCTTTCCCCCTTCCTTTCTGTGTCTCCTG  
CCTCATCGGCCTGCCATGACCTGCAGCCAAGCCCAGCCCCGTGGGGAAGGGGAGAAAGTGGGG  
GATGGCTAAGAAAGCTGGGAGATAGGGAACAGAAGAGGGTAGTGGGTGGGCTAGGGGGGCTGC  
CTTATTTAAAGTGGTTGTTTATGATTCTTATACTAATTTATACAAAGATATTAAGGCCCTGTT  
CATTAAAGAAATTGTTCCCTTCCCCTGTGTTCAATGTTTGTAAAGATTGTTCTGTGTAAATATG  
TCTTTATAATAAACAGTTAAAAGCTGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

31/168

**FIGURE 31**

GTTTGAATTCCTTCAACTATACCCACAGTCCAAAAGCAGACTCACTGTGTCCCAGGCTACCCAG  
TTCCTCCAAGCAAGTCATTTCCCTTATTTAACCGATGTGTCCCTCAAACACCTGAGTGCTACT  
CCCTATTTGCATCTGTTTTGATAAATGATGTTGACA~~C~~CCTCCACCGAATTCTAAGTGGAATCA  
TGTCGGGAAGAGATAACAATCCTTGGCCTGTGTATCCTCGCATTAGCCTTGTCTTTGGCCATGA  
TGTTTACCTTCAGATTCATCACCACCCTTCTGGTTCACATTTTCATTTTCATTGGTTATTTTGG  
GATTGTTGTTTGTCTGCGGTGTTTTATGGTGGCTGTATTATGACTATAACCAACGACCTCAGCA  
TAGAATTGGACACAGAAAGGGAAAATATGAAGTGCGTGCTGGGGTTTGCTATCGTATCCACAG  
GCATCACGGCAGTGCTGCTCGTCTTGATTTTTGTTCTCAGAAAGAGAATAAAATTGACAGTTG  
AGCTTTTCCAAATCACAAATAAAGCCATCAGCAGTGCTCCCTTCCTGCTGTTCCAGCCACTGT  
GGACATTTGCCATCCTCATTTTCTTCTGGGTCCCTCTGGGTGGCTGTGCTGCTGAGCCTGGGAA  
CTGCAGGAGCTGCCCAGGTTATGGAAGGCGGCCAAGTGGAATATAAGCCCCTTTCGGGCATTC  
GGTACATGTGGTCGTACCATTTAATTGGCCTCATCTGGACTAGTGAATTCATCCTTGCGTGCC  
AGCAAATGACTATAGCTGGGGCAGTGGTACTTGTTATTTCAACAGAAGTAAAAATGATCCTC  
CTGATCATCCCATCCTTTTCGTCTCTCTCCATTCTCTTCTTCTACCATCAAGGAACCGTTGTGA  
AAGGGTCATTTTTAATCTCTGTGGTGAGGATTCCGAGAATCATTGTGTCATGTACATGCAAAACG  
CACTGAAAGAACAGCAGCATGGTGCATTGTCCAGGTACCTGTTCCGATGCTGCTACTGCTGTT  
TCTGGTGTCTTGACAAATACCTGCTCCATCTCAACCAGAATGCATATACTACAACCTGCTATTA  
ATGGGACAGATTTCTGTACATCAGCAAAAGATGCATTCAAAATCTTGTCCAAGAACTCAAGTC  
ACTTTACATCTATTAACCTGCTTTGGAGACTTCATAATTTTTCTAGGAAAGGTGTTAGTGGTGT  
GTTTCACTGTTTTTTGGAGGACTCATGGCTTTTAACTACAATCGGGCATTCCAGGTGTGGGCAG  
TCCCTCTGTTATTGGTAGCTTTTTTTGCCTACTTAGTAGCCCATAGTTTTTTTATCTGTGTTTG  
AAACTGTGCTGGATGCACTTTTCCTGTGTTTTGCTGTTGATCTGGAAACAAATGATGGATCGT  
CAGAAAAGCCCTACTTTATGGATCAAGAATTTCTGAGTTTCGTAAAAAGGAGCAACAAATTAA  
ACAATGCAAGGGCACAGCAGGACAAGCACTCATTAAGGAATGAGGAGGGGAACAGAACTCCAGG  
CCATTGTGAGATTAGATACCCATTTAGGTATCTGTACCTGGAAAACATTTCCCTTCTAAGAGCCA  
TTTACAGAATAGAAGATGAGACCACTAGAGAAAAGTTAGTGAATTTTTTTTTTAAAGACCTAA  
TAAACCCTATTCTTCCTCAAAA

[illegible]

35/168

**FIGURE 35**

CCGAGCACAGGAGATTGCCTGCGTTTAGGAGGTGGCTGCGTTGTGGGAAAAGCTATCAAGGAA  
GAAATTGCCAAACCATGTCTTTTTTTCTGTTTTTCAGAGTAGTTCACAACAGATCTGAGTGTTT  
TAATTAAGCATGGAATACAGAAAACAACAAAAAAGCTTAAGCTTTAATTTTCATCTGGAATTCCA  
CAGTTTTCTTAGCTCCCTGGACCCGGTTGACCTGTTGGCTCTTCCCGCTGGCTGCTCTATCAC  
GTGGTGCTCTCCGACTACTCACCCCGAGTGTAAGAACCTTCGGCTCGCGTGCTTCTGAGCTG  
CTGTGGATGGCCTCGGCTCTCTGGACTGTCCTTCCGAGTAGGATGTCACTGAGATCCCTCAAA  
TGGAGCCTCCTGCTGCTGTCACTCCTGAGTTTCTTTGTGATGTGGTACCTCAGCCTTCCCCAC  
TACAATGTGATAGAACGCGTGAAGTGGATGTACTTCTATGAGTATGAGCCGATTTACAGACAA  
GACTTTCACTTCACACTTCGAGAGCATTCAAAGTCTCTCATCAAAATCCATTTCTGGTCATT  
CTGGTGACCTCCCACCCTTCAGATGTGAAAGCCAGGCAGGCCATTAGAGTTACTTGGGGTGAA  
AAAAAGTCTTGGTGGGGATATGAGGTTCTTACATTTTTCTTATTAGGCCAAGAGGCTGAAAAG  
GAAGACAAAATGTTGGCATTGTCCTTAGAGGATGAACACCTTCTTTATGGTGACATAATCCGA  
CAAGATTTTTTAGACACATATAATAACCTGACCTTGAAAACCATTATGGCATTGAGGTGGGTA  
ACTGAGTTTTGCCCAATGCCAAGTACGTAATGAAGACAGACACTGATGTTTTTCATCAATACT  
GGCAATTTAGTGAAGTATCTTTTAAACCTAAACCACTCAGAGAAGTTTTTCACAGGTTATCCT  
CTAATTGATAATTATTCCTATAGAGGATTTTACCACAAAACCCATATTTCTTACCAGGAGTAT  
CCTTTCAAGGTGTTCCCTCCATACTGCAGTGGGTTGGGTTATATAATGTCCAGAGATTTGGTG  
CCAAGGATCTATGAAATGATGGGTCACGTAAAACCCATCAAGTTTGAAGATGTTTATGTCGGG  
ATCTGTTTGAATTTATTAAAAGTGAACATTCATATTCCAGAAGACACAAATCTTTTCTTTCTA  
TATAGAATCCATTTGGATGTCTGTCAACTGAGACGTGTGATTGCAGCCCATGGCTTTTCTTCC  
AAGGAGATCATCACTTTTTTGGCAGGTCATGCTAAGGAACACCACATGCCATTATTAACTTCAC  
ATTCTACAAAAGCCTAGAAAGGACAGGATACCTTGTGGAAAGTGTTAAATAAAGTAGGTACTG  
TGGAAAATTCATGGGGAGGTGAGTGTGCTGGCTTACACTGAACTGAACTCATGAAAAACCCA  
GACTGGAGACTGGAGGGTTACACTTGTGATTTATTAGTCAGGCCCTTCAAAGATGATATGTGG  
AGGAATTAAATATAAAGGAATTGGAGGTTTTTGCTAAAGAAATTAATAGGACCAAACAATTTG  
GACATGTCATTCTGTAGACTAGAATTTCTTAAAAGGGTGTTACTGAGTTATAAGCTCACTAGG  
CTGTAAAAACAAAACAATGTAGAGTTTTATTTATTGAACAATGTAGTCACTTGAAGGTTTTGT  
GTATATCTTATGTGGATTACCAATTTAAAAATATATGTAGTTCTGTGTCAAAAACTTCTTCA  
CTGAAGTTATACTGAACAAAATTTTACCTGTTTTTGGTCATTTATAAAGTACTTCAAGATGTT  
GCAGTATTTACAGTTATTATTATTAAAATTACTTCAACTTTGTGTTTTTAAATGTTTTGAC  
GATTTCAATACAAGATAAAAAGGATAGTGAATCATTCTTTACATGCAAACATTTTCCAGTTAC  
TTAACTGATCAGTTTATTATTGATACATCACTCCATTAATGTAAAGTCATAGGTCATTATTGC  
ATATCAGTAATCTCTTGGACTTTGTTAAATATTTTACTGTGGTAATATAGAGAAGAATTAAAG  
CAAGAAAATCTGAAA

### FIGURE 37

CGCTCGGGCACCAGCCGCGGCAAGGATGGAGCTGGGTTCCTGGACGCAGTTGGGGCTCACTTTTCTTCAGCTCCTTCTCATCTCGTCCTTGCCAAGAGAGTACACAGTCATTAATGAAGCCTGCCCTGGAGCAGAGTGGAATATCATGTGTCGGGAGTGCTGTGAATATGATCAGATTGAGTGCCTCTGCCCCGGAAGAGGGAAGTCGTGGGTTATACCATCCCCTTGCTGCAGGAATGAGGAGAATGAGTGTGACTCCTGCCTGATCCACCCAGGTTGTACCATCTTTGAAAACCTGCAAGAGCTGCCGAAATGGCTCATGGGGGGGTACCTTGGATGACTTCTATGTGAAGGGGTTCTACTGTGCAGAGTGCCGAGCAGGCTGGTACGGAGGAGACTGCATGCGATGTGGCCAGGTTCTGCGAGCCCCAAAGGGTCAGATTTTGTGGAAGCTATCCCCTAAATGCTCACTGTGAATGGACCATTTCATGCTAAACCTGGGTTTGTTCATCCAATAAGATTTGTTCATGTTGAGTCTGGAGTTTGACTACATGTGCCAGTATGACTATGTTGAGGTTTCGTGATGGAGACAACCGCGATGCCAGATCATCAAGCGTGTCTGTGGCAACGAGCGGCCAGCTCCTATCCAGAGCATAGGATCCTCACTCCACGTCCTCTTCCACTCCGATGGCTCCAAGAATTTTGACGGTTTCCATGCCATTTATGAGGAGATCACAGCATGCTCCTCATCCCCCTTGTTCATGACGGCACGTGCGTCCTTGACAAGGCTGGATCTTACAAGTGTGCCTGCTTGGCAGGCTATACGGGCAGCGCTGTGAAAATCTCCTTGAAGAAAGAACTGCTCAGACCCTGGGGGCCAGTCAATGGGTACCAGAAATAACAGGGGGCCCTGGGCTTATCAACGGACGCCATGCTAAAATTGGCACCGTGGTGTCTTCTTTTGTAAACAACCTCTATGTTCTTAGTGGCAATGAGAAAAGAACTTGCCAGCAGAATGGAGAGTGGTCAGGGAAACAGCCCATCTGCATAAAAGCCTGCCGAGAACCAGATTTTCAGACCTGGTGAGAAGGAGAGTTCTTCCGATGCAGGTTCAAGTCAAGGGAGACACCATTACACCAGCTATACTCAGCGGCCTTCAGCAAGCAGAACTGCAGAGTGCCCTACCAAGAAGCCAGCCCTTCCCTTTGGAGATCTGCCCATGGGATACCAACATCTGCATACCCAGCTCCAGTATGAGTGCATCTCACCCTTCTACCGCCGCTGGGCAGCAGCAGGAGGACATGTCTGAGGACTGGGAAGTGGAGTGGGCGGGCACCATCCTGCATCCCTATCTGCGGGAAATTGAGAACATCACTGCTCCAAAGACCCAAGGGTTGCGCTGGCCGTGGCAGGCAGC'CATCTACAGGAGGACCAGCGGGGTGCATGACGGCAGCCTACACAAGGGAGCGTGGTTCCCTAGTCTGCAGCGGTGCCTGGTGAATGAGCGCACTGTGGTGGTGGCTGCCCACTGTGTTACTGACCTGGGGAAGGTCACCATGATCAAGACAGCAGACCTGAAAGTTGTTTTGGGAAATTCTACCGGGATGATGACCGGGATGAGAAGACCATCCAGAGCCTACAGATTTCTGCTATCATTCTGCATCCCAACTATGACCCCATCCTGCTTGATGCTGACATCGCCATCCTGAAGCTCCTAGACAAGGCCCCGTATCAGCACCCGAGTCCAGCCCATCTGCCTCGCTGCCAGTCGGGATCTCAGCACTTCCTTCCAGGAGTCCCACATCACTGTGGCTGGCTGGAATGTCTGGCAGACGTGAGGAGCCCTGGCTTCAAGAACGACACACTGCGCTCTGGGGTGGTCAGTGTGGTGGACTCGCTGCTGTGTGAGGAGCAGCATGAGGACCATGGCATCCCAGTGAGTGTCACTGATAACATGTTCTGTGCCAGCTGGGAACCCACTGCCCTTCTGATATCTGCACTGCAGAGACAGGAGGCATCGCGGCTGTGTCTTCCCAGGACGAGCATCTCCTGAGCCACGCTGGCATCTGATGGGACTGGTCAGCTGGAGCTATGATAAAACATGCAGCCACAGGCTCTCCACTGCCTTACCAAGGTGCTGCCTTTTAAAGACTGGATTGAAAGAAATATGAAATGAACCATGCTCATGCACTCCTTGAGAAGTGTTTCTGTATATCCGTCTGTACGTGTGTCAATTGCGTGAAGCAGTGTGGGCCTGAAGTGTGATTTGGCCTGTGAACTTGGCTGTGCCAGGGCTTCTGACTTCAGGGACAAA

**FIGURE 39**

GGTTCCTACATCCTCTCATCTGAGAATCAGAGAGCATAATCTTCTTACGGGCCCCGTGATTTATTAACGTGGCTTA  
ATCTGAAGGTTCTCAGTCAAATTCTTTGTGATCTACTGATTGTGGGGGCATGGCAAGGTTTGCTTAAAGGAGCTT  
GGCTGGTTTGGGCCCTTGTAGCTGACAGAAGGTGGCCAGGGAGAATGCAGCACACTGCTCGGAGAAATGAAGGCGC  
TTCTGTTGCTGGTCTTGCCCTTGGCTCAGTCCTGCTAACTACATTGACAATGTGGGCAACCTGCACTTCCTGTATT  
CAGAACTCTGTAAAGGTGCCTCCCACTACGGCCTGACCAAAGATAGGAAGAGGCGCTCACAAGATGGCTGTCCAG  
ACGGCTGTGCGAGCCTCACAGCCACGGCTCCCTCCCCAGAGGTTTCTGCAGCTGCCACCATCTCCTTAATGACAG  
ACGAGCCTGGCCTAGACAACCCTGCCTACGTGTCCTCGGCAGAGGACGGGCAGCCAGCAATCAGCCCAGTGGACT  
CTGGCCGGAGCAACCGAACTAGGGCACGGCCCTTTGAGAGATCCACTATTAGAAGCAGATCATTTAAAAAATAA  
ATCGAGCTTTGAGTGTTCTTCGAAGGACAAAGAGCGGGAGTGCAGTTGCCAACCATGCCGACCAGGGCAGGGAAA  
ATTCTGAAAACACCACTGCCCCGAAGTCTTTCCAAGGTTGTACCACCTGATTCCAGATGGTGAAATTACCAGCA  
TCAAGATCAATCGAGTAGATCCAGTGAAAGCCTCTCTATTAGGCTGGTGGGAGGTAGCGAAACCCCACTGGTCC  
ATATCATTATCCAACACATTTATCGTGATGGGGTGATCGCCAGAGACGGCCGGCTACTGCCAGGAGACATCATTC  
TAAAGGTCAACGGGATGGACATCAGCAATGTCCCTCACAACCTACGCTGTGCGTCTCCTGCGGCAGCCCTGCCAGG  
TGCTGTGGCTGACTGTGATGCGTGAACAGAAGTTCGCGAGCAGGAACAATGGACAGGCCCGGATGCCTACAGAC  
CCCGAGATGACAGCTTTCATGTGATTCTCAACAAAAGTAGCCCCGAGGAGCAGCTTGGAATAAAACTGGTGCGCA  
AGGTGGATGAGCCTGGGGTTTTTCATCTTCAATGTGCTGGATGGCGGTGTGGCATATCGACATGGTCAGCTTGAGG  
AGAATGACCGTGTGTTAGCCATCAATGGACATGATCTTCGATATGGCAGCCCAGAAAGTGCGGCTCATCTGATTC  
AGGCCAGTGAAAGACGTGTTACCTCGTGTGTCGCGCAGGTTTCGGCAGCGGAGCCCTGACATCTTTCAGGAAG  
CCGGCTGGAACAGCAATGGCAGCTGGTCCCCAGGGCCAGGGGAGAGGAGCAACACTCCCAAGCCCCTCCATCCTA  
CAATTACTTGTGATGAGAAGGTGGTAAATATCCAAAAGACCCCCGGTGAATCTCTCGGCATGACCGTTCGAGGGG  
GAGCATCACATAGAGAATGGGATTTGCCTATCTATGTGTCATCAGTGTTGAGCCCGGAGGAGTCATAAGCAGAGATG  
GAAGAATAAAAACAGGTGACATTTTGTGTAATGTGGATGGGGTCGAAGTACAGAGGTGAGCCGGAGTGAGGCAG  
TGGCATTATTGAAAAGAACATCATCCTCGATAGTACTCAAAGCTTTGGAAGTCAAAGAGTATGAGCCCCAGGAAG  
ACTGCAGCAGCCCAGCAGCCCTGGACTCCAACCACAACATGGCCCCACCCAGTGACTGGTCCCCATCCTGGGTCA  
TGTGGCTGGAATTACCACGGTGTCTGTATAACTGTAAAGATATTGTATTACGAAGAAACACAGCTGGAAGTCTGG  
GCTTCTGCATTGTAGGAGGTTATGAAGAATAAATGGAACAAACCTTTTTTTCATCAAATCCATTGTTGAAGGAA  
CACCAGCATAAATGATGGAAGAATTAGATGTGGTGATATTCTTCTTGCTGTCAATGGTAGAAGTACATCAGGAA  
TGATACATGCTTGCTTGCAAGACTGCTGAAAGAACTTAAAGGAAGAATTACTCTAACTATTGTTTCTTGGCCTG  
GCACTTTTTTATTAGAAATCAATGATGGGTGAGAGGAAAACAGAAAAATCACAAATAGGCTAAGAAGTTGAAACACT  
ATATTTATCTTGTGAGTTTTTATATTTAAAGAAAGAATACATTGTAAAAATGTCAGGAAAAGTATGATCATCTAA  
TGAAAGCCAGTTACACCTCAGAAAATATGATTCCAAAAAATTAATACTACTAGTTTTTTTTTTCAGTGTGGAGGAT  
TTCTCATTACTCTACAACATTGTTTATATTTTTTCTATTCAATAAAAAGCCCTAAAACAATAAATGATTGATT  
TGTATACCCCACTGAATTCAGCTGATTTAAATTTAAATTTGGTATATGCTGAAGTCTGCCAAGGGTACATTAT  
GGCCATTTTTTAATTTACAGCTAAAATATTTTTTAAATGCATTGCTGAGAAACGTTGCTTTCATCAAACAAGAAT  
AAATATTTTTTCAGAAGTTAAA

41/168

**FIGURE 41**

ACCAGGCATTGTATCTTCAGTTGTCATCAAGTTCGCAATCAGATTGGAAAAGCTCAACTTGAA  
GCTTTCTTGCCCTGCAGTGAAGCAGAGAGATAGATATTATTCACGTAATAAAAAACATGGGCTT  
CAACCTGACTTTCCACCTTTTCTACAAATTCGGATTACTGTTGCTGTTGACTTTGTGCCTGAC  
AGTGGTTGGGTGGGCCACCAGTAACTACTTCGTGGGTGCCATTCAAGAGATTCCTAAAGCAAA  
GGAGTTCATGGCTAATTTCCATAAGACCCTCATTTTGGGGAAGGGAAAACTCTGACTAATGA  
AGCATCCACGAAGAAGGTAGAACTTGACAACTGTCCTTCTGTGTCTCCTTACCTCAGAGGCCA  
GAGCAAGCTCATTTTCAAACCAGATCTCACTTTGGAAGAGGTACAGGCAGAAAATCCCAAAGT  
GTCCAGAGGCCGGTATCGCCCTCAGGAATGTAAAGCTTTACAGAGGGTCGCCATCCTCGTTCC  
CCACCGGAACAGAGAGAAACACCTGATGTACCTGCTGGAACATCTGCATCCCTTCCTGCAGAG  
GCAGCAGCTGGATTATGGCATCTACGTCATCCACCAGGCTGAAGGTAAAAAGTTTAATCGAGC  
CAAACCTCTTGAATGTGGGCTATCTAGAAGCCCTCAAGGAAGAAAATTGGGACTGCTTTATATT  
CCACGATGTGGACCTGGTACCCGAGAATGACTTTAACCTTTACAAGTGTGAGGAGCATCCCAA  
GCATCTGGTGGTTGGCAGGAACAGCACTGGGTACAGGTTACGTTACAGTGGATATTTTGGGGG  
TGTTACTGCCCTAAGCAGAGAGCAGTTTTTCAAGGTGAATGGATTCTCTAACAACACTACTGGGG  
ATGGGGAGGCGAAGACGATGACCTCAGACTCAGGGTTGAGCTCCAAAGAATGAAAATTTCCCG  
GCCCCTGCCTGAAGTGGGTAAATATACAATGGTCTTCCACACTAGAGACAAAGGCAATGAGGT  
GAACGCAGAACGGATGAAGCTCTTACACCAAGTGTACAGAGTCTGGAGAACAGATGGGTTGAG  
TAGTTGTTCTTATAAATTAGTATCTGTGGAACACAATCCTTTATATATCAACATCACAGTGGA  
TTTCTGGTTTGGTGCATTGACCCTGGATCTTTTGGTGATGTTTGGGAAGAACTGATTCTTTGTTT  
GCAATAATTTTGGCCTAGAGACTTCAAATAGTAGCACACATTAAGAACCTGTTACAGCTCATT  
GTTGAGCTGAATTTTTCCTTTTGTATTTTCTTAGCAGAGCTCCTGGTGATGTAGAGTATAAA  
ACAGTTGTAACAAGACAGCTTTCTTAGTCATTTTGTATCATGAGGGTTAAATATTGTAATATGG  
ATACTTGAAGGACTTTATATAAAAGGATGACTCAAAGGATAAAATGAACGCTATTTGAGGACT  
CTGGTTGAAGGAGATTTATTTAAATTTGAAGTAATATATTATGGGATAAAAGGCCACAGGAAA  
TAAGACTGCTGAATGTCTGAGAGAACCAGAGTTGTTCTCGTCCAAGGTAGAAAGGTACGAAGA  
TACAATACTGTTATTTCATTTATCCTGTACAATCATCTGTGAAGTGGTGGTGTCAGGTGAGAAG  
GCGTCCACAAAAGAGGGGAGAAAAGGCGACGAATCAGGACACAGTGAACCTTGGGAATGAAGAG  
GTAGCAGGAGGGTGGAGTGTGCGCTGCAAAGGCAGCAGTAGCTGAGCTGGTTGCAGGTGCTGA  
TAGCCTTCAGGGGAGGACCTGCCAGGTATGCCTTCCAGTGATGCCACCAGAGAATACATTC  
TCTATTAGTTTTTAAAGAGTTTTTGTAAAATGATTTTGTACAAGTAGGATATGAATTAGCAGT  
TTACAAGTTTACATATTAATAATAATAATATGTCTATCAAATACCTCTGTAGTAAAATGTG  
AAAAAGCAAAA



43/168

**FIGURE 43**

GCTCAAGACCCAGCAGTGGGACAGCCAGACAGACGGCACGATGGCACTGAGCTCCCAGATCTG  
GGCCGCTTGCCTCCTGCTCCTCCTCCTCGCCAGCCTGACCAGTGGCTCTGTTTTCCCACA  
ACAGACGGGACAACCTTGCAGAGCTGCAACCCAGGACAGAGCTGGAGCCAGGGCCAGCTGGAT  
GCCCATGTTCCAGAGGCGAAGGAGGCGAGACACCCACTTCCCCATCTGCATTTTCTGCTGCGG  
CTGCTGTCATCGATCAAAGTGTGGGATGTGCTGCAAGACGTAGAACCTACCTGCCCTGCCCCC  
GTCCCCTCCCTTCCTTATTTATTCCTGCTGCCCCAGAACATAGGTCTTGGAATAAAATGGCTG  
GTTCTTTTGTTCCTTCCAAA  
AAA

45/168

**FIGURE 45**

GTGGCTTCATTTTCAGTGGCTGACTTCCAGAGAGCAATATGGCTGGTTCCCCAACATGCCTCAC  
CCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGCTGGT  
CGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTCCAAAGTAAAGCAAGTTGACTCTAT  
TGTCTGGACCTTCAACACAACCCCTCTTGTACCATAACAGCCAGAAGGGGGCACTATCATAGT  
GACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCCTGAAGCTCAG  
CAAAGTGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTCATCACTCCAGCA  
GCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAGCCTAAAGTCACCAT  
GGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACATGCTGCATGGAACATGG  
GGAAGAGGATGTGATTTATACCTGGAAGGCCCTGGGGCAAGCAGCCAATGAGTCCCATAATGG  
GTCCATCCTCCCCATCTCCTGGAGATGGGGAGAAAGTGATATGACCTTCATCTGCGTTGCCAG  
GAACCCTGTCAGCAGAACTTCTCAAGCCCCATCCTTGCCAGGAAGCTCTGTGAAGGTGCTGC  
TGATGACCCAGATTCTCCTCATGGTCCTCCTGTGTCTCCTGTTGGTGCCCCCTCCTGCTCAGTCT  
CTTTGTACTGGGGCTATTTCTTTGGTTTCTGAAGAGAGAGAGACAAGAAGAGTACATTGAAGA  
GAAGAAGAGAGTGGACATTTGTGCGGAAACTCCTAACATATGCCCCCATTCTGGAGAGAACAC  
AGAGTACGACACAATCCCTCACACTAATAGAACAATCCTAAAGGAAGATCCAGCAAATACGGT  
TTACTCCACTGTGGAAATACCGAAAAAGATGGAAATCCCCACTCACTGCTCACGATGCCAGA  
CACACCAAGGCTATTTGCCTATGAGAATGTTATCTAGACAGCAGTGCCTCCCTAAGTCTCT  
GCTCA

47/168

**FIGURE 47**

GGCTCGAGCGTTTCTGAGCCAGGGGTGACCATGACCTGCTGCGAAGGATGGACATCCTGCAAT  
GGATTGAGCCTGCTGGTTCTACTGCTGTTAGGAGTAGTTCTCAATGCGATACCTCTAATTGTC  
AGCTTAGTTGAGGAAGACCAATTTTCTCAAACCCCATCTCTTGCTTTGAGTGGTGGTTCCCA  
GGAATTATAGGAGCAGGTCTGATGGCCATTCCAGCAACAACAATGTCCTTGACAGCAAGAAAA  
AGAGCGTGCTGCAACAACAGAACTGGAATGTTTCTTTTCATCATTTTTTCAGTGTGATCACAGTC  
ATTGGTGCTCTGTATTGCATGCTGATATCCATCCAGGCTCTCTTAAAAGGTCCTCTCATGTGT  
AATTCTCCAAGCAACAGTAATGCCAATTGTGAATTTTCATTGAAAAACATCAGTGACATTTCAT  
CCAGAATCCTTCAACTTGCAGTGGTTTTTCAATGACTCTTGTGCACCTCCTACTGGTTTTCAAT  
AAACCCACCAGTAACGACACCATGGCGAGTGGCTGGAGAGCATCTAGTTTCCACTTCGATTCT  
GAAGAAAACAAACATAGGCTTATCCACTTCTCAGTATTTTTAGGTCTATTGCTTGTTGGAATT  
CTGGAGGTCCTGTTTGGGCTCAGTCAGATAGTCATCGGTTTCCTTGGCTGTCTGTGTGGAGTC  
TCTAAGCGAAGAAGTCAAATTGTGTAGTTTAATGGGAATAAAATGTAAGTATCAGTAGTTTGA  
AAAAAAAAA

49/168

**FIGURE 49**

ATCCGTTCTCTGCGCTGCCAGCTCAGGTGAGCCCTCGCCAAGGTGACCTCGCAGGACACTGGT  
GAAGGAGCAGTGAGGAACCTGCAGAGTCACACAGTTGCTGACCAATTGAGCTGTGAGCCTGGA  
GCAGATCCGTGGGCTGCAGACCCCGCCCCAGTGCCCTCTCCCCCTGCAGCCCTGCCCCCTCGAA  
CTGTGACATGGAGAGAGTGACCCTGGCCCTTCTCCTACTGGCAGGCCTGACTGCCTTGGAAGC  
CAATGACCCATTTGCCAATAAAGACGATCCCTTCTACTATGACTGGAAAAACCTGCAGCTGAG  
CGGACTGATCTGCGGAGGGCTCCTGGCCATTGCTGGGATCGCGGCAGTTCTGAGTGGCAAATG  
CAAATACAAGAGCAGCCAGAAGCAGCACAGTCCTGTACCTGAGAAGGCCATCCCCTCATCAC  
TCCAGGCTCTGCCACTACTTGCTTGAGCACAGGACTGGCCTCCAGGGATGGCCTGAAGCCTAAC  
ACTGGCCCCCAGCACCTCCTCCCCCTGGGAGGCCTTATCCTCAAGGAAGGACTTCTCTCCAAGG  
GCAGGCTGTTAGGCCCTTTCTGATCAGGAGGCTTCTTTATGAATTAACTCGCCCCACCACC  
CCCTCA



53/168

**FIGURE 53**

GGAGAAGAGGTTGTGTGGGACAAGCTGCTCCCGACAGAAGGATGTCGCTGCTGAGCCTGCCCT  
GGCTGGGCCTCAGACCGGTGGCAATGTCCCATGGCTACTCCTGCTGCTGGTTGTGGGCTCCT  
GGCTACTCGCCCGCATCCTGGCTTGGACCTATGCCTTCTATAACAAGTGCCGCCGGCTCCAGT  
GTTTCCCACAGCCCCCAAACGGAAGTGGTTTTGGGGTCACCTGGGCCTGATCACTCCTACAG  
AGGAGGGCTTGAAGGACTCGACCCAGATGTGCGGCCACCTATTCCCAGGGCTTTACGGTATGGC  
TGGGTCCCATCATCCCCTTCATCGTTTTATGCCACCCTGACACCATCCGGTCTATCACCAATG  
CCTCAGCTGCCATTGCACCCAAGGATAATCTCTTCATCAGGTTCTGAAGCCCTGGCTGGGAG  
AAGGGATACTGCTGAGTGGCGGTGACAAGTGGAGCCGCCACCGTCGGATGCTGACGCCCCGCT  
TCCATTTCAACATCCTGAAGTCCTATATAACGATCTTCAACAAGAGTGCAAACATCATGCTTG  
ACAAGTGGCAGCACCTGGCCTCAGAGGGCAGCAGTCGTCTGGACATGTTTGAGCACATCAGCC  
TCATGACCTTGGACAGTCTACAGAAATGCATCTTCAGCTTTGACAGCCATTGTCAGGAGAGGC  
CCAGTGAATATATTGCCACCATCTTGGAGCTCAGTGCCCTTGTAGAGAAAAGAAGCCAGCATA  
TCCTCCAGCACATGGACTTTCTGTATTACCTCTCCCATGACGGGCGGGCGCTTCCACAGGGCCT  
GCCGCCTGGTGCATGACTTCACAGACGCTGTCATCCGGGAGCGGCGTCGCACCCTCCCCACTC  
AGGGTATTGATGATTTTTTCAAAGACAAAGCCAAGTCCAAGACTTTGGATTTCAATTGATGTGC  
TTCTGCTGAGCAAGGATGAAGATGGGAAGGCATTGTCAGATGAGGATATAAGAGCAGAGGCTG  
ACACCTTCATGTTTGGAGGCCATGACACCACGGCCAGTGGCCTCTCCTGGGTCTGTACAACC  
TTGCGAGGCACCCAGAATACCAGGAGCGCTGCCGACAGGAGGTGCAAGAGCTTCTGAAGGACC  
GCGATCCTAAAGAGATTGAATGGGACGACCTGGCCCAGCTGCCCTTCCTGACCATGTGCGTGA  
AGGAGAGCCTGAGGTTACATCCCCCAGCTCCCTTCATCTCCCGATGCTGCACCCAGGACATTG  
TTCTCCCAGATGGCCGAGTCATCCCCAAAGGCATTACCTGCCTCATCGATATTATAGGGGTCC  
ATCACAACCCAACTGTGTGGCCGGATCCTGAGGTCTACGACCCCTTCCGCTTTGACCCAGAGA  
ACAGCAAGGGGAGGTCACCTCTGGCTTTTATTCTTTCTCCGCAGGGCCCAGGAACTGCATCG  
GGCAGGCGTTTCGCCATGGCGGAGATGAAAGTGGTCCTGGCGTTGATGCTGCTGCACTTCCGGT  
TCCTGCCAGACCACACTGAGCCCCGCAGGAAGCTGGAATTGATCATGCGCGCCGAGGGCGGGC  
TTTGGCTGCGGGTGGAGCCCCCTGAATGTAGGCTTGCAGTGACTTTCTGACCCATCCACCTGTT  
TTTTTGCAGATTGTCATGAATAAAACGGTGCTGTCAA

55/168

**FIGURE 55**

ATCGCATCAATTGGGAGTACCATCTTCCTCATGGGACCAGTGAAACAGCTGAAGCGAATGTTT  
GAGCCTACTCGTTTGATTGCAACTATCATGGTGCTGTTGTGTTTTGCACTTACCCTGTGTTCT  
GCCTTTTGGTGGCATAACAAGGGACTTGCACTTATCTTCTGCATTTTGCAGTCTTTGGCATTG  
ACGTGGTACAGCCTTTCCTTCATACCATTGCAAGGGATGCTGTGAAGAAGTGTTTTGCCGTG  
TGTCTTGCATAAATTCATGGCCAGTTTTATGAAGCTTTGGAAGGCACTATGGACAGAAGCTGGT  
GGACAGTTTTGTAACTATCTTCGAAACCTCTGTCTTACAGACATGTGCCTTTTATCTTGCAGC  
AATGTGTTGCTTGTGATTGGAACATTTGAGGGTTACTTTTGGGAAGCAACAATACATTCTCGAA  
CCTGAATGTCAGTAGCACAGGATGAGAAGTGGGTCTGTATCTTGTGGAGTGGAATCTTCCTC  
ATGTACCTGTTTCCTCTCTGGATGTTGTCCCACTGAATTCCCATGAATACAAACCTATTCAGC  
AACAGCAA  
AAAAAAAAAAAAAA

[illegible]



59/168

**FIGURE 59**

GGAAGGCAGCGGCAGCTCCACTCAGCCAGTACCCAGATACGCTGGGAACCTTCCCCAGCC**ATG**  
GCTTCCCTGGGGCAGATCCTCTTCTGGAGCATAATTAGCATCATCATTATTCTGGCTGGAGCA  
ATTGCACTCATCATTGGCTTTGGTATTTTCAGGGAGACACTCCATCACAGTCACTACTGTCGCC  
TCAGCTGGGAACATTGGGGAGGATGGAATCCTGAGCTGCACTTTTGAACCTGACATCAAACCTT  
TCTGATATCGTGATAACAATGGCTGAAGGAAGGTGTTTTAGGCTTGGTCCATGAGTTCAAAGAA  
GGCAAAGATGAGCTGTCGGAGCAGGATGAAATGTTTCAGAGGCCGGACAGCAGTGTTTGCTGAT  
CAAGTGATAGTTGGCAATGCCTCTTTGCGGCTGAAAAACGTGCAACTCACAGATGCTGGCACC  
TACAAATGTTATATCATCACTTCTAAAGGCAAGGGGAATGCTAACCTTGAGTATAAAACTGGA  
GCCTTCAGCATGCCGGAAGTGAATGTGGACTATAATGCCAGCTCAGAGACCTTGCGGTGTGAG  
GCTCCCCGATGGTTCCCCCAGCCACAGTGGTCTGGGCATCCCAAGTTGACCAGGGAGCCAAC  
TTCTCGGAAGTCTCCAATACCAGCTTTGAGCTGAACTCTGAGAATGTGACCATGAAGGTTGTG  
TCTGTGCTCTACAATGTTACGATCAACAACACATACTCCTGTATGATTGAAAATGACATTGCC  
AAAGCAACAGGGGATATCAAAGTGACAGAATCGGAGATCAAAGGCGGAGTCACCTACAGCTG  
CTAAACTCAAAGGCTTCTCTGTGTGTCTCTTCTTTTCTTTGCCATCAGCTGGGCACTTCTGCCT  
CTCAGCCCTTACCTGATGCTAAAA**TAA**TGTGCCTTGGCCACAAAAAAGCATGCAAAGTCATTG  
TTACAACAGGGATCTACAGAACTATTTACCACCAGATATGACCTAGTTTTATATTTCTGGGA  
GGAAATGAATTCATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAAACAAAAAGAAGCC  
AAAAGCAGAAGGCTCCAATATGAACAAGATAAATCTATCTTCAAAGACATATTAGAAGTTGGG  
AAAATAATTCATGTGAACTAGACAAGTGTGTTAAGAGTGATAAGTAAATGCACGTGGAGACA  
AGTGCATCCCCAGATCTCAGGGACCTCCCCCTGCCTGTCACCTGGGGAGTGAGAGGACAGGAT  
AGTGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTGTAATGTTGCTCTGAGGAAGCC  
CCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCACAAATTAAGCTGTAGTATGTAC  
CCTAAGACGCTGCTAATTGACTGCCACTTCGCAACTCAGGGGCGGCTGCATTTTAGTAATGGG  
TCAAATGATTCACTTTTTATGATGCTTCCAAAGGTGCCTTGGCTTCTCTTCCCAACTGACAAA  
TGCCAAAGTTGAGAAAAATGATCATAATTTAGCATAAACAGAGCAGTCGGGGACACCGATTT  
TATAAATAAACTGAGCACCTTCTTTTTAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAA

61/168

**FIGURE 61**

TGACGTCAGAATCACCATGGCCAGCTATCCTTACCGGCAGGGCTGCCCAGGAGCTGCAGGACA  
AGCACCAGGAGCCCCCTCCGGGTAGCTACTACCCTGGACCCCCCAATAGTGAGGGGCAGTATGG  
TAGTGGGCTACCCCCTGGTGGTGGTTATGGGGGTCTTGCCCCTGGAGGGCCTTATGGACCACC  
AGCTGGTGGAGGGCCCTATGGACACCCCAATCCTGGGATGTTCCCCTCTGGAACCTCCAGGAGG  
ACCATATGGCGGTGCAGCTCCCGGGGGGCCCTATGGTCAGCCACCTCCAAGTTCCTACGGTGC  
CCAGCAGCCTGGGCTTTATGGACAGGGTGGCGCCCCCTCCCAATGTGGATCCTGAGGCCTACTC  
CTGGTTCCAGTCGGTGGACTCAGATCACAGTGGCTATATCTCCATGAAGGAGCTAAAGCAGGC  
CCTGGTCAACTGCAATTGGTCTTCATTCAATGATGAGACCTGCCTCATGATGATAAACATGTT  
TGACAAGACCAAGTCAGGCCGCATCGATGTCTACGGCTTCTCAGCCCTGTGGAAATTCATCCA  
GCAGTGGAAGAACCTCTTCCAGCAGTATGACCGGGACCGCTCGGGCTCCATTAGCTACACAGA  
GCTGCAGCAAGCTCTGTCCCAAATGGGCTACAACCTGAGCCCCAGTTCACCCAGCTTCTGGT  
CTCCCGCTACTGCCCACGCTCTGCCAATCCTGCCATGCAGCTTGACCGCTTCATCCAGGTGTG  
CACCCAGCTGCAGGTGCTGACAGAGGCCTTCCGGGAGAAGGACACAGCTGTACAAGGCAACAT  
CCGGCTCAGCTTCGAGGACTTCGTCACCATGACAGCTTCTCGGATGCTATGACCCAACCATCT  
GTGGAGAGTGGAGTGCACCAGGGACCTTTCTGGCTTCTTAGAGTGAGAGAAGTATGTGGACA  
TCTCTTCTTTTCTGTCCCTCTAGAAGAACATTCTCCCTTGCTTGATGCAACACTGTTCCAAA  
AGAGGGTGGAGAGTCCTGCATCATAGCCACCAAATAGTGAGGACCGGGGCTGAGGCCACACAG  
ATAGGGGCCTGATGGAGGAGAGGATAGAAGTTGAATGTCCTGATGGCCATGAGCAGTTGAGTG  
GCACAGCCTGGCACCAGGAGCAGGTCTTGTAATGGAGTTAGTGTCCAGTCAGCTGAGCTCCA  
CCCTGATGCCAGTGGTGAGTGTTCATCGGCCTGTTACCGTTAGTACCTGTGTTCCCTCACCAG  
GCCATCCTGTCAAACGAGCCCATTTTCTCCAAAGTGGAATCTGACCAAGCATGAGAGAGATCT  
GTCTATGGGACCAGTGGCTTGGATTCTGCCACACCCATAAATCCTTGTGTGTTAACTTCTAGC  
TGCTTGGGGCTGGCCCTGCTCAGACAAATCTGCTCCCTGGGCATCTTTGGCCAGGCTTCTGCC  
CCCTGCAGCTGGGACCCCTCACTTGCTGCCATGCTCTGCTCGGCTTCAGTCTCCAGGAGACA  
GTGGTCACCTCTCCCTGCCAATACTTTTTTTAATTTGCATTTTTTTTTCATTTGGGGCCAAAAG  
TCCAGTGAAATTGTAAGCTTCAATAAAAGGATGAAACTCTGA

63/168

**FIGURE 63**

CAGGATGCAGGGCCGCGTGGCAGGGAGCTGCGCTCCTCTGGGCCTGCTCCTGGTCTGTCTTCA  
TCTCCCAGGCCTCTTTGCCCCGAGCATCGGTGTTGTGGAGGAGAAAGTTTCCCAAACTTCGG  
GACCAACTTGCCTCAGCTCGGACAACCTTCCTCCACTGGCCCCCTCTAACTCTGAACATCCGCA  
GCCCCGCTCTGGACCCTAGGTCTAATGACTTGGCAAGGGTTCCTCTGAAGCTCAGCGTGCCTCC  
ATCAGATGGCTTCCCACCTGCAGGAGGTTCTGCAGTGCAGAGGTGGCCTCCATCGTGGGGGCT  
GCCTGCCATGGATTCTTGGCCCCCTGAGGATCCTTGGCAGATGATGGCTGCTGCGGCTGAGGA  
CCGCCTGGGGGAAGCGCTGCCTGAAGAACTCTTTACCTCTCCAGTGCTGCGGCCCTCGCTCC  
GGGCAGTGGCCCTTTGCCTGGGGAGTCTTCTCCCGATGCCACAGGCCTCTCACCTGAGGCTTC  
ACTCCTCCACCAGGACTCGGAGTCCAGACGACTGCCCCGTTCTAATTCACTGGGAGCCGGGGG  
AAAAATCCTTTCCCAACGCCCTCCCTGGTCTCTCATCCACAGGGTTCTGCCTGATCACCCCTG  
GGGTACCCTGAATCCCAGTGTGTCCTGGGGAGGTGGAGGCCCTGGGACTGGTTGGGGAACGAG  
GCCCATGCCACACCCTGAGGGAATCTGGGGTATCAATAATCAACCCCCAGGTACCAGCTGGGG  
AAATATTAATCGGTATCCAGGAGGCAGCTGGGGAAATATTAATCGGTATCCAGGAGGCAGCTG  
GGGGAATATTAATCGGTATCCAGGAGGCAGCTGGGGGAATATTCATCTATAACCAGGTATCAA  
TAACCCATTTCTCCTGGAGTTCTCCGCCCTCCTGGCTCTTCTTGGAACATCCCAGCTGGCTT  
CCCTAATCCTCCAAGCCCTAGGTGTCAGTGGGGCTAGAGCACGATAGAGGGAAACCCAAACATT  
GGGAGTTAGAGTCCTGCTCCCGCCCCCTTGCTGTGTGGGCTCAATCCAGGCCCTGTAAACATGT  
TTCCAGCACTATCCCCACTTTTCAGTGCCTCCCCTGCTCATCTCCAATAAAATAAAAGCACTT  
ATGAA  
AAA

65/168

**FIGURE 65**

AAGGAGAGGCCACCGGGACTTCAGTGTCTCCTCCATCCCAGGAGCGCAGTGGCCACTATGGGG  
TCTGGGCTGCCCCCTTGTCTCCTCTTGACCCTCCTTGGCAGCTCACATGGAACAGGGCCGGGT  
ATGACTTTGCAACTGAAGCTGAAGGAGTCTTTTCTGACAAATTCCTCCTATGAGTCCAGCTTC  
CTGGAATTGCTTGAAAAGCTCTGCCTCCTCCTCCATCTCCCTTCAGGGACCAGCGTCACCCTC  
CACCATGCAAGATCTCAACACCATGTTGTCTGCAACACATGACAGCCATTGAAGCCTGTGTCC  
TTCTTGGCCCCGGGCTTTTGGGCCGGGGATGCAGGAGGCAGGCCCCGACCCTGTCTTTCAGCAG  
GCCCCACCCTCCTGAGTGGCAATAAATAAAATTCGGTATGCTG

67/168

**FIGURE 67**

ACGGACCGAGGGTTCGAGGGAGGGACACGGACCAGGAACCTGAGCTAGGTCAAAGACGCCCCG  
GCCAGGTGCCCCGTCGCAGGTGCCCCTGGCCGGAGATGCGGTAGGAGGGGCGAGCGCGAGAAG  
CCCCTTCCTCGGCGCTGCCAACCCGCCACCCAGCCCATGGCGAACCCCGGGCTGGGGCTGCTT  
CTGGCGCTGGGCCTGCCGTTCTGCTGGCCCGCTGGGGCCGAGCCTGGGGGCAAATACAGACC  
ACTTCTGCAAATGAGAATAGCACTGTTTTGCCTTCATCCACCAGCTCCAGCTCCGATGGCAAC  
CTGCGTCCGGAAGCCATCACTGCTATCATCGTGGTCTTCTCCCTCTTGGCTGCCTTGCTCCTG  
GCTGTGGGGCTGGCACTGTTGGTGCGGAAGCTTCGGGAGAAGCGGCAGACGGAGGGCACCTAC  
CGGCCCAGTAGCGAGGAGCAGTTCTCCCATGCAGCCGAGGCCCGGGCCCCTCAGGACTCCAAG  
GAGACGGTGCAGGGCTGCCTGCCCATCTAGGTCCCCTCTCCTGCATCTGTCTCCCTTCATTGC  
TGTGTGACCTTGGGGAAAGGCAGTGCCCTCTCTGGGCAGTCAGATCCACCCAGTGCTTAATAG  
CAGGGAAGAAGGTACTTCAAAGACTCTGCCCCTGAGGTCAAGAGAGGATGGGGCTATTCACTT  
TTATATATTTATATAAAATTAGTAGTGAGATGTAAAAAAAAAAAAAAAAAAAAA

## FIGURE 69

[illegible]

71/168

**FIGURE 71**

CTCCTTAGGTGGAAACCCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATAACGTCCCCGGGCAAGGGG  
TGACAACAGGTGTCTATCTTTTTGATCTCGTGTGTGGCTGCCTTCTTCAAGGAAAGACGCCAAGGTAATTTT  
GACCCAGAGGAGCAATGATGTAGCCACCTCCTAACCTTCCCTTCTTGAACCCCAAGTTATGCCAGGATTTACTAG  
AGAGTGTCAACTCAACCAGCAAGCGGCTCCTTCGGCTTAACCTGTGGTTGGAGGAGAGAACCTTTGTGGGGCTGC  
GTTCTCTTAGCAGTGCTCAGAAGTGACTTGCCTGAGGGTGGACCAGAAGAAAGGAAAGGTCCCCTCTTGCTGTTG  
GCTGCACATCAGGAAGGCTGTGATGGGAATGAAGGTGAAAACCTTGGAGATTTCACTTCAGTCATTGCTTCTGCCT  
GCAAGATCATCTTTAAAAGTAGAGAAGCTGCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAA  
GGAAATGGATGCAAGCAGCTCCGGGGGCCCCAACGCATGCTTCCTGTGGTCTAGCCCAGGGAAGCCCTTCCGTG  
GGGGCCCCGGCTTTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCTGAATGATGATGGTTCCGCCGGGG  
CTGCTTGGCTGGATTTCCCGGGTGGTGGTTTTGCTGGTGCTCCTCTGCTGTGCTATCTCTGTCTGTACATGTTG  
GCCTGCACCCCAAAAGGTGACGAGGAGCAGCTGGCACTGCCAGGGCCAACAGCCCCACGGGGAAGGAGGGGTAC  
CAGGCCGCTCCTTCAGGAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCGGCAGATCGCACAGCTC  
AAGGAGGAGCTGCAGGAGAGGAGTGAGCAGCTCAGGAATGGGCAGTACCAAGCCAGCGATGCTGCTGGCCTGAGG  
CTGGACAGGAGCCCCCAGAGAAAACCCAGGCCGACCTCCTGGCCTTCTCTGACTCGCAGGTGGACAAGGCAGAG  
GTGAATGCTGGCGTCAAGCTGGCCACAGAGTATGCAGCAGTGCCTTTCGATAGCTTTACTCTACAGAAGGTGTAC  
CAGCTGGAGACTGGCCTTACC CGCCACCCCGAGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAA  
GCCATTGAATCAGCCTTGGAGACCCTGAACAATCCTGCAGAGAACAGCCCCAATCACCGTCTTACACGGCCTCT  
GATTTTCATAGAAGGGATCTACCGAACAGAAAGGGACAAAGGGACATTGTATGAGCTCACCTTCAAAGGGGACCAC  
AAACACGAATTCAAACGGCTCATCTTATTTTCGACCATTTCAGCCCCATCATGAAAGTGAAAAATGAAAAGCTCAAC  
ATGGCCAACACGCTTATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCCGGCAGTTTCATGCAGAAT  
TTCAGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGGAAAGAAGAAATAAT  
GAAGTCAAAGGAATACTTGAAAACACTTCCAAAGCTGCCAACTTCAGGAACCTTACCTTCATCCAGCTGAATGGA  
GAATTTTCTCGGGGAAGGGACTTGATGTTGGAGCCCGCTTCTGGAAGGGAAGCAACGTCCTTCTTTTTCTGT  
GATGTGGACATCTACTTCACATCTGAATTCCTCAATACGTGTAGGCTGAATACACAGCCAGGGAAGAAGGTATTT  
TATCCAGTTCTTTTTCAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTCCCTCCCTTGGAAACAG  
CAGCTGGTCATAAAGAAGGAAACTGGATTTTGGAGAGACTTTGGATTTGGGATGACGTGTCACTATCGGTGAGAC  
TTCATCAATATAGGTGGGTTTGTCTGGACATCAAAGGCTGGGGCGGAGAGGATGTGCACCTTTATCGCAAGTAT  
CTCCACAGCAACCTCATAGTGGTACGGACGCTGTGCGAGGACTCTTCCACCTCTGGCATGAGAAGCGCTGCATG  
GACGAGCTGACCCCGAGCAGTACAAGATGTGCATGCAGTCCAAGGCCATGAACGAGGCATCCCACGGCCAGCTG  
GGCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTTCGCAACAGAAACAGAAGACAAGTAGCAAAAAACA  
**TGA**ACTCCCAGAGAAGGATTGTGGGAGACACTTTTTCTTTCTTTTGAATTAAGTGGCTGCAACAGAGA  
AAAGACTTCCATAAAGGACGACAAAAGAATTGGACTGATGGGTAGAGATGAGAAAGCCTCCGATTTCTCTGT  
TGGGCTTTTTTACAACAGAAATCAAATCTCCGCTTTGCCTGCAAAAGTAACCCAGTTGCACCCTGTGAAGTGTCT  
GACAAAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTGTGGAGGTTTTGATGGTGTTTACAATACACTGAGA  
CCTGTTGTTTTGTGTGCTCATTGAAATATTATGATTTAAGAGCAGTTTTGTAAAAAATTCATTAGCATGAAAGG  
CAAGCATATTTCTCCTCATATGAATGAGCCTATCAGCAGGGCTCTAGTTTCTAGGAATGCTAAAATATCAGAAGG  
CAGGAGAGGAGATAGGCTTATTATGATACTAGTGAGTACATTAAGTAAAATAAATGGACCAGAAAAGAAAAGAA  
ACCATAAATATCGTGTCTATATTTTCCCCAAGATTAACCAAAAATAATCTGCTTATCTTTTGGTTGTCTTTTAA  
CTGCTCCGTTTTTTTTCTTTTATTTAAAAATGCACTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTAC  
CACTTTGCAAGCCTTACAAGAGAGCACAAGTTGGCCTACATTTTTATATTTTTTAAGAAGATACTTTGAGATGCA  
TTATGAGAACTTTCAAGTTCAAGCATCAAATGATGCCATATCCAAGGACATGCCAATGCTGATTCTGTGAGGC  
ACTGAATGTCAGGCATTGAGACATAGGGAAGGAATGGTTTGTACTAATACAGACGTACAGATACTTTCTCTGAAG  
AGTATTTTTCGAAGAGGAGCAACTGAACACTGGAGGAAAAGAAAATGACACTTTCTGCTTTACAGAAAAGGAACT  
CATTCAGACTGGTGATATCGTGATGTACCTAAAAGTCAGAAACCACATTTTCTCCTCAGAAGTAGGGACCGCTTT  
CTTACCTGTTTAAATAAACCAGGTATACCGTGTGAACCAACAATCTTTTCAAACAGGGTGCTCCTCCTGG  
CTTCTGGCTTCCATAAGAAGAAATGGAGAAAAATATATATATATATATATATTTGTGAAAGATCAATCCATCTG  
CCAGAATCTAGTGGGATGGAAGTTTTTGTGCTACATGTTATCCACCCAGGCCAGGTGGAAGTAACTGAATATTTT  
TTAAATTAAGCAGTTCTACTCAATACCAAGATGCTTCTGAAAATTGCATTTTATTACCATTTCAAACATTTTTT  
TAAAAATAAATACAGTTAACATAGAGTGGTTTCTTCATTTCATGTGAAAATTATTAGCCAGCACCAGATGCATGAG  
CTAATTATCTCTTTGAGTCTTTGCTTCTGTTGCTCACAGTAAACTCATTGTTTAAAAGCTTCAAGAACATTCAA  
GCTGTTGGTGTGTTAAAAAATGCATTGTATTGATTTGTACTGGTAGTTTATGAAATTTAATTAACACAGGCCA  
TGAATGGAAGGTGGTATTGCACAGCTAATAAAATATGATTTGTGGATATGAA

73/168

**FIGURE 73**

GAGACTGCAGAGGGAGATAAAGAGAGAGGGCAAAGAGGCAGCAAGAGATTTGTCCTGGGGATC  
CAGAAACCCATGATACCCTACTGAACACCGAATCCCCTGGAAGCCCACAGAGACAGAGACAGC  
AAGAGAAGCAGAGATAAATACTCACGCCAGGAGCTCGCTCGCTCTCTCTCTCTCTCTCA  
CTCCTCCCTCCCTCTCTCTCTGCTGTCCTAGTCCTCTAGTCCTCAAATTTCCCAGTCCCCTGC  
ACCCCTTCCTGGGACACTATGTTGTTCTCCGCCCTCCTGCTGGAGGTGATTTGGATCCTGGCT  
GCAGATGGGGGTCAACACTGGACGTATGAGGGCCACATGGTCAGGACCATTGGCCAGCCTCT  
TACCCTGAGTGTGGAAACAATGCCAGTCGCCATCGATATTCAGACAGACAGTGTGACATTT  
GACCCTGATTTGCCTGCTCTGCAGCCCCACGGATATGACCAGCCTGGCACCGAGCCTTTGGAC  
CTGCACAACAATGGCCACACAGTGCAACTCTCTCTGCCCTCTACCCTGTATCTGGGTGGACTT  
CCCCGAAAATATGTAGCTGCCCAGCTCCACCTGCACTGGGGTCAGAAAGGATCCCCAGGGGGG  
TCAGAACACCAGATCAACAGTGAAGCCACATTTGCAGAGCTCCACATTGTACATTATGACTCT  
GATTCCTATGACAGCTTGAGTGAGGCTGCTGAGAGGCCTCAGGGCCTGGCTGTCCTGGGCATC  
CTAATTGAGGTGGGTGAGACTAAGAATATAGCTTATGAACACATTCTGAGTCACTTGCATGAA  
GTCAGGCATAAAGATCAGAAGACCTCAGTGCCTCCCTTCAACCTAAGAGAGCTGCTCCCCAAA  
CAGCTGGGGCAGTACTTCCGCTACAATGGCTCGCTCACAACCTCCCCCTTGCTACCAGAGTGTG  
CTCTGGACAGTTTTTTATAGAAGGTCCCAGATTTCAATGGAACAGCTGGAAAAGCTTCAGGGG  
ACATTGTTCTCCACAGAAGAGGAGCCCTCTAAGCTTCTGGTACAGAACTACCGAGCCCTTCAG  
CCTCTCAATCAGCGCATGGTCTTTGCTTCTTTTCATCCAAGCAGGATCCTCGTATAACCACAGGT  
GAAATGCTGAGTCTAGGTGTAGGAATCTTGGTTGGCTGTCTCTGCCTTCTCCTGGCTGTTTAT  
TTCATTGCTAGAAAGATTCCGGAAGAAGAGGCTGGAAAACCGAAAGAGTGTGGTCTTCACCTCA  
GCACAAGCCACGACTGAGGCATTAAATTCCCTTCTCAGATACCATGGATGTGGATGACTTCCCTT  
CATGCCTATCAGGAAGCCTCTAAAATGGGGTGTAGGATCTGGCCAGAAACACTGTAGGAGTAG  
TAAGCAGATGTCCTCCTTCCCCTGGACATCTCTTAGAGAGGAATGGACCCAGGCTGTCATTCC  
AGGAAGAAGTGCAGAGCCTTCAGCCTCTCCAAACATGTAGGAGGAAATGAGGAAATCGCTGTG  
TTGTTAATGCAGAGANCAAACCTCTGTTTAGTTGCAGGGGAAGTTTGGGATATACCCCAAAGTC  
CTCTACCCCTCACTTTTATGGCCCTTTCCCTAGATATACTGCGGGATCTCTCCTTAGGATAA  
AGAGTTGCTGTTGAAGTTGTATATTTTTGATCAATATATTTGGAAATTAAAGTTTCTGACTTT



75/168

**FIGURE 75**

TGCCGCTGCCGCCGCTGCTGCTGTTGCTCCTGGCGGCGCCTTGGGGACGGGCAGTTCCCTGTG  
TCTCTGGTGGTTTGCCTAAACCTGCAAACATCACCTTCTTATCCATCAACATGAAGAATGTCC  
TACAATGGACTCCACCAGAGGGTCTTCAAGGAGTTAAAGTTACTTACACTGTGCAGTATTTCA  
TCACAAATTGGCCCACCAGAGGTGGCACTGACTACAGATGAGAAGTCCATTTCTGTTGTCCTG  
ACAGCTCCAGAGAAGTGGAAGAGAAATCCAGAAGACCTTCCTGTTTCCATGCAACAAATATAC  
TCCAATCTGAAGTATAACGTGTCTGTGTTGAATACTAAATCAAACAGAACGTGGTCCCAGTGT  
GTGACCAACCACACGCTGGTGCTCACCTGGCTGGAGCCGAACACTCTTTACTGCGTACACGTG  
GAGTCCTTCGTCCCAGGGCCCCCTCGCCGTGCTCAGCCTTCTGAGAAGCAGTGTGCCAGGACT  
TTGAAAGATCAATCATCAGAGTTCAAGGCTAAATCATCTTCTGGTATGTTTTGCCCATATCT  
ATTACCGTGTTTCTTTTTTCTGTGATGGGCTATTCCATCTACCGATATATCCACGTTGGCAAA  
GAGAAACACCCAGCAAATTTGATTTTGGTTTATGGAAATGAATTTGACAAAAGATTCTTTGTG  
CCTGCTGAAAAAATCGTGATTAACTTTATCACCTCAATATCTCGGATGATTCTAAAATTTCT  
CATCAGGATATGAGTTTACTGGGAAAAAGCAGTGATGTATCCAGCCTTAATGATCCTCAGCCC  
AGCGGGAACCTGAGGCCCCCTCAGGAGGAAGAGGAGGTGAAACATTTAGGGTATGCTTCGCAT  
TTGATGGAAATTTTTTGTGACTCTGAAGAAAACACGGAAGGTACTTCTCTCACCCAGCAAGAG  
TCCCTCAGCAGAACAAATACCCCCGGATAAAACAGTCATTGAATATGAATATGATGTCAGAACC  
ACTGACATTTGTGCGGGGCCTGAAGAGCAGGAGCTCAGTTTGCAGGAGGAGGTGTCCACACAA  
GGAACATTATTGGAGTCGCAGGCAGCGTTGGCAGTCTTGGGCCCCGAAACGTTACAGTACTCA  
TACACCCCTCAGCTCCAAGACTTAGACCCCCTGGCGCAGGAGCACACAGACTCGGAGGAGGGG  
CCGGAGGAAGAGCCATCGACGACCCTGGTCGACTGGGATCCCCAACTGGCAGGCTGTGTATT  
CCTTCGCTGTCCAGCTTCGACCAGGATTCAGAGGGCTGCGAGCCTTCTGAGGGGGATGGGCTC  
GGAGAGGAGGGTCTTCTATCTAGACTCTATGAGGAGCCGGCTCCAGACAGGCCACCAGGAGAA  
AATGAAACCTATCTCATGCAATTCATGGAGGAATGGGGGTATATGTGCAGATGGAAAACTGA  
TGCCAACACTTCCTTTTGCCTTTTGTTCCTGTGCAAACAAGTGAGTCACCCCTTTGATCCCA  
GCCATAAAGTACCTGGGATGAAAGAAGTTTTTTCCAGTTTGTGAGTGTCTGTGAGAATTACTT  
ATTTCTTTTCTCTATTCTCATAGCACGTGTGTGATTGGTTCATGCATGTAGGTCTCTTAACAA  
TGATGGTGGGCCTCTGGAGTCCAGGGGCTGGCCGGTTGTTCTATGCAGAGAAAGCAGTCAATA  
AATGTTTGCCAGACTGGGTGCAGAATTTATTTCAGGTGGGTGT

77/168

**FIGURE 77**

GAGGAGCGGGCCGAGGACTCCAGCGTGCCCAGGTCTGGCATCCTGCACTTGCTGCCCTCTGAC  
ACCTGGGAAGATGGCCGGCCCCGTGGACCTTCACCCTTCTCTGTGGTTTGCTGGCAGCCACCTT  
GATCCAAGCCACCCTCAGTCCCAGTGCAGTTCTCATCCTCGGCCCAAAGTCATCAAAGAAAA  
GCTGACACAGGAGCTGAAGGACCACAACGCCACCAGCATCCTGCAGCAGCTGCCGCTGCTCAG  
TGCCATGCGGGAAAAGCCAGCCGGAGGCATCCCTGTGCTGGGCAGCCTGGTGAACACCGTCCT  
GAAGCACATCATCTGGCTGAAGGTCATCACAGCTAACATCCTCCAGCTGCAGGTGAAGCCCTC  
GGCCAATGACCAGGAGCTGCTAGTCAAGATCCCCCTGGACATGGTGGCTGGATTCAACACGCC  
CCTGGTCAAGACCATCGTGGAGTTCCACATGACGACTGAGGCCCAAGCCACCATCCGCATGGA  
CACCAGTGCAAGTGGCCCCACCCGCTGGTCCTCAGTGACTGTGCCACCAGCCATGGGAGCCT  
GCGCATCCAAGTCTGTATAAGCTCTCCTTCCTGGTGAACGCCTTAGCTAAGCAGGTCATGAA  
CCTCCTAGTGCCATCCCTGCCCAATCTAGTGAAAAACCAAGCTGTGTCCCGTGATCGAGGCTTC  
CTTCAATGGCATGTATGCAGACCTCCTGCAGCTGGTGAAGGTGCCCATTTCCCTCAGCATTGA  
CCGTCTGGAGTTTGACCTTCTGTATCCTGCCATCAAGGGTGACACCATTACAGCTCTACCTGGG  
GGCCAAGTTGTTGGACTCACAGGGAAAGGTGACCAAGTGGTTCAATAACTCTGCAGCTTCCCT  
GACAATGCCCACCCTGGACAACATCCCGTTAGCCTCATCGTGAGTCAGGACGTGGTGAAGC  
TGCAGTGGCTGCTGTGCTCTCTCCAGAAGAATTCATGGTCCTGTTGGACTCTGTGCTTCCCTGA  
GAGTGCCCATCGGCTGAAGTCAAGCATCGGGCTGATCAATGAAAAGGCTGCAGATAAGCTGGG  
ATCTACCCAGATCGTGAAGATCCTAACTCAGGACACTCCCGAGTTTTTTATAGACCAAGGCCA  
TGCCAAGGTGGCCCAACTGATCGTGCTGGAAGTGTTCCTCCAGTGAAGCCCTCCGCCCTTT  
GTTACCCCTGGGCATCGAAGCCAGCTCGGAAGCTCAGTTTTTACACCAAAGGTGACCAACTTAT  
ACTCAACTTGAATAACATCAGCTCTGATCGGATCCAGCTGATGAACTCTGGGATTGGCTGGTT  
CCAACCTGATGTTCTGAAAAACATCATCACTGAGATCATCCACTCCATCCTGCTGCCGAACCA  
GAATGGCAAATTAAGATCTGGGGTCCCAGTGTGATTGGTGAAGGCCTTGGGATTTCGAGGCAGC  
TGAGTCCTCACTGACCAAGGATGCCCTTGTGCTTACTCCAGCCTCCTTGTGGAAACCCAGCTC  
TCCTGTCTCCAGTGAAGACTTGGATGGCAGCCATCAGGGAAGGCTGGGTCCCAGCTGGGAGT  
ATGGGTGTGAGCTCTATAGACCATCCCTCTCTGCAATCAATAAACACTTGCCTGTGAAAAA

79/168

**FIGURE 79**

GAGAGAAGTCAGCCTGGCAGAGAGACTCTGAAATGAGGGATTAGAGGTGTTCAAGGAGCAAGA  
GCTTCAGCCTGAAGACAAGGGAGCAGTCCCTGAAGACGCTTCTACTGAGAGGTCTGCCATGGC  
CTCTCTTGGCCTCCAACCTTGTGGGCTACATCCTAGGCCTTCTGGGGCTTTTGGGCACACTGGT  
TGCCATGCTGCTCCCCAGCTGGAAAACAAGTTCTTATGTCGGTGCCAGCATTGTGACAGCAGT  
TGGCTTCTCCAAGGGCCTCTGGATGGAATGTGCCACACACAGCACAGGCATCACCCAGTGTGA  
CATCTATAGCACCCCTTCTGGGCCTGCCCCGCTGACATCCAGGCTGCCCAGGCCATGATGGTGAC  
ATCCAGTGCAATCTCCTCCCTGGCCTGCATTATCTCTGTGGTGGGCATGAGATGCACAGTCTT  
CTGCCAGGAATCCCGAGCCAAAGACAGAGTGGCGGTAGCAGGTGGAGTCTTTTTCATCCTTGG  
AGGCCTCCTGGGATTCATTCTGTTGCCTGGAATCTTCATGGGATCCTACGGGACTTCTACTC  
ACCACTGGTGCCTGACAGCATGAAATTTGAGATTGGAGAGGCTCTTTACTTGGGCATTATTTT  
TTCCCTGTTCTCCCTGATAGCTGGAATCATCCTCTGCTTTTCTGCTCATCCCAGAGAAATCG  
CTCCAACCTACTACGATGCCTACCAAGCCCAACCTCTTGCCACAAGGAGCTCTCCAAGGCCTGG  
TCAACCTCCCAAAGTCAAGAGTGAGTTCAATTCCTACAGCCTGACAGGGTATGTGTGAAGAAC  
CAGGGGCCAGAGCTGGGGGGTGGCTGGGTCTGTGAAAAACAGTGGACAGCACCCCGAGGGCCA  
CAGGTGAGGGACACTACCACTGGATCGTGTGAGAAGGTGCTGCTGAGGATAGACTGACTTTGG  
CCATTGGATTGAGCAAAGGCAGAAATGGGGGCTAGTGTAACAGCATGCAGGTTGAATTGCCAA  
GGATGCTCGCCATGCCAGCCTTTCTGTTTTCTCACCTTGCTGCTCCCCTGCCCTAAGTCCCC  
AACCCTCAACTTGAAACCCCATTCCTTAAGCCAGGACTCAGAGGATCCCTTTGCCCTCTGGT  
TTACCTGGGACTCCATCCCCAAACCCACTAATCACATCCCCTGACTGACCCTCTGTGATCAA  
AGACCCTCTCTCTGGCTGAGGTTGGCTCTTAGCTCATTGCTGGGGATGGGAAGGAGAAGCAGT  
GGCTTTTGTGGGCATTGCTCTAACCTACTTCTCAAGCTTCCCTCCAAAGAACTGATTGGCCC  
TGGAACCTCCATCCCCTCTTGTATGACTCCACAGTGTCCAGACTAATTTGTGCATGAACTG  
AAATAAAACCATCCTACGGTATCCAGGGAACAGAAAGCAGGATGCAGGATGGGAGGACAGGAA  
GGCAGCCTGGGACATTTAAAAAATA

81/168

**FIGURE 81**

CCCACGCGTCCGCGCCTCTCCCTTCTGCTGGACCTTCCTTCGTCTCTCCATCTCTCCCTCCTT  
TCCCCGCGTTCTCTTTCCACCTTTCTCTTCTTCCCACCTTAGACCTCCCTTCCTGCCCCTCCTT  
TCCTGCCCACCGCTGCTTCCTGGCCCTTCTCCGACCCCGCTCTAGCAGCAGACCTCCTGGGGT  
CTGTGGGTTGATCTGTGGCCCCCTGTGCCTCCGTGTCCTTTTCGTCTCCCTTCCTCCCGACTCC  
GCTCCCGGACCAGCGGCCTGACCCTGGGGAAAGGATGGTTCCCGAGGTGAGGGTCTCTCCTC  
CTTGCTGGGACTCGCGCTGCTCTGGTTCCCCCTGGACTCCACGCTCGAGCCCGCCCAGACAT  
GTTCTGCCTTTTCCATGGGAAGAGATACTCCCCGGCGAGAGCTGGCACCCCTACTTGAGGCC  
ACAAGGCCTGATGTACTGCCTGCGCTGTACCTGCTCAGAGGGCGCCCATGTGAGTTGTTACCG  
CCTCCACTGTCCGCCTGTCCACTGCCCCCAGCCTGTGACGGAGCCACAGCAATGCTGTCCCAA  
GTGTGTGGAACCTCACACTCCCTCTGGACTCCGGGGCCCCACCAAAGTCCTGCCAGCACAAACGG  
GACCATGTACCAACACGGAGAGATCTTCAGTGCCCATGAGCTGTTCCCCCTCCCGCCTGCCCAA  
CCAGTGTGTCCTCTGCAGCTGCACAGAGGGCCAGATCTACTGCGGCCTCACAACCTGCCCCGA  
ACCAGGCTGCCCAGCACCCCTCCCCTGCCCAGACTCCTGCTGCCAAGCCTGCAAAGATGAGGC  
AAGTGAGCAATCGGATGAAGAGGACAGTGTGCAGTCGCTCCATGGGGTGAGACATCCTCAGGA  
TCCATGTTCCAGTGATGCTGGGAGAAAGAGAGGCCCGGGCACCCAGCCCCACTGGCCTCAG  
CGCCCCCTCTGAGCTTCATCCCTCGCCACTTCAGACCCAAGGGAGCAGGCAGCACAACTGTCAA  
GATCGTCCTGAAGGAGAAACATAAGAAAGCCTGTGTGCATGGCGGGAAGACGTACTCCACGG  
GGAGGTGTGGCACCCGGCCTTCCGTGCCTTCGGCCCCCTTGCCCTGCATCCTATGCACCTGTGA  
GGATGGCCGCCAGGACTGCCAGCGTGTGACCTGTCCCACCGAGTACCCCTGCCGTACCCCCGA  
GAAAGTGGCTGGGAAGTGCTGCAAGATTTGCCCAGAGGACAAAGCAGACCCTGGCCACAGTGA  
GATCAGTTCTACCAGGTGTCCCAAGGCACCGGGCCGGGTCTCGTCCACACATCGGTATCCCC  
AAGCCCAGACAACCTGCGTCGCTTTGCCCTGGAACACGAGGCCTCGGACTTGGTGGAGATCTA  
CCTCTGGAAGCTGGTAAAAGATGAGGAACTGAGGCTCAGAGAGGTGAAGTACCTGGCCCAAG  
GCCACACAGCCAGAATCTTCCACTTGACTCAGATCAAGAAAGTCAGGAAGCAAGACTTCCAGA  
AAGAGGCACAGCACTTCCGACTGCTCGCTGGCCCCCACGAAGGTCACTGGAACGTCTTCCTAG  
CCCAGACCCTGGAGCTGAAGGTCACGGCCAGTCCAGACAAAGTGACCAAGACATAACAAAGAC  
CTAACAGTTGCAGATATGAGCTGTATAATTGTTGTTATTATATATTAATAAATAAGAAGTTGC  
ATTACCCTCAAAAAAAAAAAAAAAAAAAAAA

83/168

**FIGURE 83**

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTTGCCCTCCGCTCACGCAGA  
GCCTCTCCGTGGCTTCCGCACCTTGAGCATTAGGCCAGTTCTCCTCTTCTCTAATCCATCC  
GTCACCTCTCCTGTCATCCGTTTCCATGCCGTGAGGTCCATTACAGAACACATCCATGGCTC  
TCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGCAGGTGTTTGGGC  
CAGACAAGCCTGTCCAGGCCTTGGTGGGGGAGGACGCAGCATTCTCCTGTTTCCTGTCTCCTA  
AGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGCCAGTTCTCTAGCGTGGTCCACC  
TCTACAGGGACGGAAGGACCAGCCATTTATGCAGATGCCACAGTATCAAGGCAGGACAAAAC  
TGGTGAAGGATTCTATTGCGGAGGGGCGCATCTCTCTGAGGCTGGAAAACATTACTGTGTGG  
ATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGTCTTACTACCAGAAGGCCATCTGGGAGC  
TACAGGTGTCAGCACTGGGCTCAGTTCCTCTCATTTCCATCACGGGATATGTTGATAGAGACA  
TCCAGCTACTCTGTCACTCCTCGGGCTGGTTCCCCCGGCCACAGCGAAGTGGAAGGTCCAC  
AAGGACAGGATTTGTCCACAGACTCCAGGACAAACAGAGACATGCATGGCCTGTTTGATGTGG  
AGATCTCTCTGACCGTCCAAGAGAACGCCGGGAGCATATCCTGTTCCATGCGGCATGCTCATC  
TGAGCCGAGAGGTGGAATCCAGGGTACAGATAGGAGATACCTTTTTTCGAGCCTATATCGTGGC  
ACCTGGCTACCAAAGTACTGGGAATACTCTGCTGTGGCCTATTTTTTGGCATTGTTGGACTGA  
AGATTTTCTTCTCCAAATTCAGTGGAATAATCCAGGCGGAACTGGACTGGAGAAGAAAGCAGC  
GACAGGCAGAATTGAGAGACGCCCGGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGG  
CTCACCCGAAGCTCTGCGTTTCTGATCTGAAAACGTGAACCCATAGAAAAGCTCCCCAGGAGG  
TGCCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGAGTTTCCAAGCAG  
GGAAACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGCGTGGGAGTGTGCCGGG  
ATGATGTGGACAGGAGGAAGGAGTACGTGACTTTGTCTCCCGATCATGGGTACTGGGTCCTCA  
GACTGAATGGAGAACATTTGTATTTACATTAAATCCCCGTTTTATCAGCGTCTTCCCCAGGA  
CCCCACCTACAAAATAGGGGTCTTCTGGACTATGAGTGTGGGACCATCTCCTTCTTCAACA  
TAAATGACCAGTCCCTTATTTATACCCTGACATGTCGGTTTGAAGGCTTATTGAGGCCCTACA  
TTGAGTATCCGTCCTATAATGAGCAAAATGGAACCTCCCATAGTCATCTGCCCAGTCACCCAGG  
AATCAGAGAAAGAGGCCTCTTGGCAAAGGGCCTCTGCAATCCCAGAGACAAGCAACAGTGAGT  
CCTCCTCACAGGCAACCACGCCCTTCTCCCCAGGGGTGAAATGTAGGATGAATCACATCCCA  
CATTCTTCTTTAGGGATATTAAGGTCTCTCTCCCAGATCCAAAGTCCCGCAGCAGCCGGCCAA  
GGTGGCTTCCAGATGAAGGGGACTGGCCTGTCCACATGGGAGTCAGGTGTCATGGCTGCCCT  
GAGCTGGGAGGGAAGAAGGCTGACATTACATTTAGTTTGCTCTCACTCCATCTGGCTAAGTGA  
TCTTGAAATACCACCTCTCAGGTGAAGAACCGTCAGGAATTCCCATCTCACAGGCTGTGGTGT  
AGATTAAGTAGACAAGGAATGTGAATAATGCTTAGATCTTATTGATGACAGAGTGTATCCTAA  
TGGTTTGTTCATTATATTACACTTTCAGTAAAAAA

85/168

**FIGURE 85**

AACAGACGTTCCCTCGCGGCCCTGGCACCTCTAACCCAGACATGCTGCTGCTGCTGCTGCCC  
CTGCTCTGGGGGAGGGAGAGGGCGGAAGGACAGACAAGTAAACTGCTGACGATGCAGAGTTCC  
GTGACGGTGCAGGAAGGCCTGTGTGTCCATGTGCCCTGCTCCTTCTCCTACCCCTCGCATGGC  
TGGATTTACCCTGGCCCAGTAGTTTCATGGCTACTGGTTCCGGGAAGGGGCCAATACAGACCAG  
GATGCTCCAGTGGCCACAAACAACCCAGCTCGGGCAGTGTGGGAGGAGACTCGGGACCGATTC  
CACCTCCTTGGGGACCCACATACCAAGAATTGCACCCTGAGCATCAGAGATGCCAGAAGAAGT  
GATGCGGGGAGATACTTCTTTTCGTATGGAGAAAGGAAGTATAAAATGGAATTATAAACATCAC  
CGGCTCTCTGTGAATGTGACAGCCTTGACCCACAGGCCCAACATCCTCATCCCAGGCACCCTG  
GAGTCCGGCTGCCCCCAGAATCTGACCTGCTCTGTGCCCTGGGCCTGTGAGCAGGGGACACCC  
CCTATGATCTCCTGGATAGGGACCTCCGTGTCCCCCCTGGACCCCTCCACCACCCGCTCCTCG  
GTGCTCACCCCTCATCCCACAGCCCCAGGACCATGGCACCAGCCTCACCTGTCAGGTGACCTTC  
CCTGGGGCCAGCGTGACCACGAACAAGACCGTCCATCTCAACGTGTCCTACCCGCCTCAGAAC  
TTGACCATGACTGTCTTCCAAGGAGACGGCACAGTATCCACAGTCTTGGGAAATGGCTCATCT  
CTGTCACTCCCAGAGGGCCAGTCTCTGCGCCTGGTCTGTGCAGTTGATGCAGTTGACAGCAAT  
CCCCCTGCCAGGCTGAGCCTGAGCTGGAGAGGCCTGACCCTGTGCCCTCACAGCCCTCAAAC  
CCGGGGGTGCTGGAGCTGCCTTGGGTGCACCTGAGGGATGCAGCTGAATTCACCTGCAGAGCT  
CAGAACCCTCTCGGCTCTCAGCAGGTCTACCTGAACGTCTCCCTGCAGAGCAAAGCCACATCA  
GGAGTGA CT CAGGGGGTGGTCGGGGGAGCTGGAGCCACAGCCCTGGTCTTCCTGTCCTTCTGC  
GTCATCTTCGTTGTAGTGAGGTCCTGCAGGAAGAAATCGGCAAGGCCAGCAGCGGGCGTGGGA  
GATACGGGCATAGAGGATGCAAACGCTGTCAGGGGTTTCAGCCTCTCAGGGGCCCTGACTGAA  
CCTTGGGCAGAAGACAGTCCCCCAGACCAGCCTCCCCAGCTTCTGCCCCTCCTCAGTGGGG  
GAAGGAGAGCTCCAGTATGCATCCCTCAGCTTCCAGATGGTGAAGCCTTGGGACTCGCGGGGA  
CAGGAGGCCACTGACACCGAGTACTCGGAGATCAAGATCCACAGATGAGAACTGCAGAGACT  
CACCCCTGATTGAGGGATCACAGCCCCCTCCAGGCAAGGGAGAAGTCAGAGGCTGATTCTTGTAG  
AATTAACAGCCCTCAACGTGATGAGCTATGATAACACTATGAATTATGTGCAGAGTGAAAAGC  
ACACAGGCTTTAGAGTCAAAGTATCTCAAACCTGAATCCACACTGTGCCCTCCCTTTTATTTT  
TTTAACTAAAAGACAGACAAATTCCTA

87/168

**FIGURE 87**

AGAAAGCTGCACTCTGTTGAGCTCCAGGGCGCAGTGGAGGGAGGGAGTGAAGGAGCTCTCTGT  
ACCCAAGGAAAGTGCAGCTGAGACTCAGACAAGATTACAATGAACCAACTCAGCTTCCTGCTG  
TTTCTCATAGCGACCACCAGAGGATGGAGTACAGATGAGGCTAATACTTACTTCAAGGAATGG  
ACCTGTTCTTCGTCTCCATCTCTGCCCAGAAGCTGCAAGGAAATCAAAGACGAATGTCCTAGT  
GCATTTGATGGCCTGTATTTTCTCCGCACTGAGAATGGTGTATCTACCAGACCTTCTGTGAC  
ATGACCTCTGGGGGTGGCGGCTGGACCCTGGTGGCCAGCGTGCATGAGAATGACATGCGTGGG  
AAGTGCACGGTGGGCGATCGCTGGTCCAGTCAGCAGGGCAGCAAAGCAGACTACCCAGAGGGG  
GACGGCAACTGGGCCAACTACAACACCTTTGGATCTGCAGAGGCGGCCACGAGCGATGACTAC  
AAGAACCCTGGCTACTACGACATCCAGGCCAAGGACCTGGGCATCTGGCACGTGCCCAATAAG  
TCCCCCATGCAGCACTGGAGAAACAGCTCCCTGCTGAGGTACCGCACGGACACTGGCTTCCTC  
CAGACACTGGGACATAATCTGTTTGGCATCTACCAGAAATATCCAGTGAAATATGGAGAAGGA  
AAGTGTGGACTGACAACGGCCCGGTGATCCCTGTGGTCTATGATTTTGGCGACGCCCAGAAA  
ACAGCATCTTATTACTCACCTATGGCCAGCGGGAATTCAGTGCGGGATTTGTTTCAGTTCAGG  
GTATTTAATAACGAGAGAGCAGCCAACGCCTTGTGTGCTGGAATGAGGGTCACCGGATGTAAC  
ACTGAGCATCACTGCATTGGTGGAGGAGGATACTTTCCAGAGGCCAGTCCCCAGCAGTGTGGA  
GATTTTTCTGGTTTTGATTGGAGTGGATATGGAACATCATGTTGGTTACAGCAGCAGCCGTGAG  
ATAACTGAGGCAGCTGTGCTTCTATTCTATCGTTGAGAGTTTTGTGGGAGGGAACCCAGACCT  
CTCCTCCCAACCATGAGATCCCAAGGATGGAGAACAACCTTACCCAGTAGCTAGAATGTTAATG  
GCAGAAGAGAAAACAATAAATCATATTGACTCAAGAAAAAA

89/168

**FIGURE 89**

CTAGATTTGTCGGCTTGCGGGGAGACTTCAGGAGTCGCTGTCTCTGAACTTCCAGCCTCAGAG  
ACCGCCGCCCTTGTCCCCGAGGGGCCATGGGCCGGGTCTCAGGGCTTGTGCCCTCTCGCTTCCT  
GACGCTCCTGGCGCATCTGGTGGTCGTCATCACCTTATTCTGGTCCCGGGACAGCAACATACA  
GGCCTGCCTGCCTCTCACGTTACCCCCGAGGAGTATGACAAGCAGGACATTCAGCTGGTGGC  
CGCGCTCTCTGTCACCCTGGGCCTCTTTGCAGTGGAGCTGGCCGGTTTCCTCTCAGGAGTCTC  
CATGTTCAACAGCACCCAGAGCCTCATCTCCATTGGGGCTCACTGTAGTGCATCCGTGGCCCT  
GTCCTTCTTCATATTCGAGCGTTGGGAGTGCCTACGTATTGGTACATTTTTGTCTTCTGCAG  
TGCCCTTCCAGCTGTCACTGAAATGGCTTTATTCGTCACCGTCTTTGGGCTGAAAAAGAAACC  
CTTCTGATTACCTTCATGACGGGAACCTAAGGACGAAGCCTACAGGGGCAAGGGCCGCTTCGT  
ATTCCTGGAAGAAGGAAGGCATAGGCTTCGGTTTTCCCCTCGGAAACTGCTTCTGCTGGAGGA  
TATGTGTTGGAATAATTACGTCTTGAGTCTGGGATTATCCGCATTGTATTTAGTGCTTTGTAA  
TAAAATATGTTTTGTAGTAACATTAAGACTTATATACAGTTTTAGGGGACAATTAAAAAAAAA  
AAA



91/168

**FIGURE 91**

CTGGGACCCCGAAAAGAGAAGGGGAGAGCGAGGGGACGAGAGCGGAGGAGGAAGATGCAACTG  
ACTCGCTGCTGCTTCGTGTTCTGGTGCAGGGTAGCCTCTATCTGGTCATCTGTGGCCAGGAT  
GATGGTCCTCCCGGCTCAGAGGACCCTGAGCGTGATGACCACGAGGGGCCAGCCCCGGCCCCGG  
GTGCCTCGGAAGCGGGGCCACATCTCACCTAAGTCCCGCCCCATGGCCAATTCCACTCTCCTA  
GGGCTGCTGGCCCCGCCTGGGGAGGCTTGGGGCATTCTTGGGCAGCCCCCAACCGCCCGAAC  
CACAGCCCCCACCCCTCAGCCAAGGTGAAGAAAATCTTTGGCTGGGGCGACTTCTACTCCAAC  
ATCAAGACGGTGGCCCTGAACCTGCTCGTCACAGGGAAGATTGTGGACCATGGCAATGGGACC  
TTCAGCGTCCACTTCCAACACAATGCCACAGGCCAGGGAAACATCTCCATCAGCCTCGTGCCC  
CCCAGTAAAGCTGTAGAGTTCCACCAGGAACAGCAGATCTTCATCGAAGCCAAGGCCTCCAAA  
ATCTTCAACTGCCGGATGGAGTGGGAGAAGGTAGAACGGGGCCGCGGACCTCGCTTTGCACC  
CACGACCCAGCCAAGATCTGCTCCCGAGACCACGCTCAGAGCTCAGCCACCTGGAGCTGCTCC  
CAGCCCTTCAAAGTCGTCTGTGTCTACATCGCCTTCTACAGCACGGACTATCGGCTGGTCCAG  
AAGGTGTGCCCAGATTACAACCTACCATAGTGATACCCCCTACTACCCATCTGGGTGACCCCGGG  
GCAGGCCACAGAGGCCAGGCCAGGGCTGGAAGGACAGGCCTGCCCATGCAGGAGACCATCTGG  
ACACCGGGCAGGGAAGGGGTGGGCCTCAGGCAGGGAGGGGGGTGGAGACGAGGAGATGCCAA  
GTGGGGCCAGGGCCAAGTCTCAAGTGGCAGAGAAAGGGTCCCAAGTGCTGGTCCCAACCTGAA  
GCTGTGGAGTGACTAGATCACAGGAGCACTGGAGGAGGAGTGGGCTCTCTGTGCAGCCTCACA  
GGGCTTTGCCACGGAGCCACAGAGAGATGCTGGGTCCCCGAGGCCTGTGGGCAGGCCGATCAG  
TGTGGCCCCAGATCAAGTCATGGGAGGAAGCTAAGCCCTTGGTTCTTGCCATCCTGAGGAAAG  
ATAGCAACAGGGAGGGGGAGATTTTCATCAGTGTGGACAGCCTGTCAACTTAGGATGGATGGCT  
GAGAGGGCTTCCTAGGAGCCAGTCAGCAGGGTGGGGTGGGGCCAGAGGAGCTCTCCAGCCCTG  
CCTAGTGGGCGCCCTGAGCCCCTTGTCGTGTGCTGAGCATGGCATGAGGCTGAAGTGGCAACC  
CTGGGGTCTTTGATGTCTTGACAGATTGACCATCTGTCTCCAGCCAGGCCACCCCTTTCCAAA  
ATTCCCTCTTCTGCCAGTACTCCCCCTGTACCACCCATTGCTGATGGCACACCCATCCTTAAG  
CTAAGACAGGACGATTGTGGTCTTCCCACACTAAGGCCACAGCCCATCCGCGTGCTGTGTGTC  
CCTCTTCCACCCCAACCCCTGCTGGCTCCTCTGGGAGCATCCATGTCCCGGAGAGGGGTCCCT  
CAACAGTCAGCCTCACCTGTCAGACCGGGGTCTCCCGGATCTGGATGGCGCCGCCCTCTCAG  
CAGCGGGCACGGGTGGGGCGGGGCCGGGCCGAGAGCATGTGCTGGATCTGTTCTGTGTGTCT  
GTCTGTGGGTGGGGGAGGGGAGGGAAGTCTTGTGAAACCGCTGATTGCTGACTTTTGTGTGA  
AGAATCGTGTCTTGGAGCAGGAAATAAAGCTTGCCCCGGGGCA

93/168

**FIGURE 93**

CGGTGGCCATGACTGCGGCCGTGTTCTTCGGCTGCGCCTTCATTGCCTTCGGGCCTGCGCTCG  
CCCTTTATGTCTTCACCATCGCCATCGAGCCGTTGCGTATCATCTTCCTCATCGCCGGAGCTT  
TCTTCTGGTTGGTGTCTCTACTGATTTTCGTCCCTTGTTTGGTTCATGGCAAGAGTCATTATTG  
ACAACAAAGATGGACCAACACAGAAATATCTGCTGATCTTTGGAGCGTTTGTCTCTGTCTATA  
TCCAAGAAATGTTCCGATTTGCATATTATAAACTCTTAAAAAAGCCAGTGAAGGTTTGAAGA  
GTATAAACCAGGTGAGACAGCACCTCTATGCGACTGCTGGCCTATGTTTCTGGCTTGGGCT  
TTGGAATCATGAGTGGAGTATTTTCCTTTGTGAATACCCTATCTGACTCCTTGGGGCCAGGCA  
CAGTGGGCATTCATGGAGATTCTCCTCAATTCTTCCTTTATTCAGCTTTCATGACGCTGGTCA  
TTATCTTGCTGCATGTATTCTGGGGCATTGTATTTTTTTGATGGCTGTGAGAAGAAAAAGTGGG  
GCATCCTCCTTATCGTTCTCCTGACCCACCTGCTGGTGTGAGCCAGACCTTCATAAGTTCTT  
ATTATGGAATAAACCTGGCGTCAGCATTTATAATCCTGGTGTGCTCATGGGCACCTGGGCATTCT  
TAGCTGCGGGAGGCAGCTGCCGAAGCCTGAAACTCTGCCTGCTCTGCCAAGACAAGAACTTTC  
TTCTTTACAACCAGCGCTCCAGATTAACCTCAGGGAACCAGCACTTCCCAAACCGCAGACTACA  
TCTTTAGAGGAAGCACAACCTGTGCCTTTTTTCTGAAAATCCCTTTTTCTGGTGGAATTGAGAAA  
GAAATAAACTATGCAGATA

95/168

**FIGURE 95**

AATTTTTCACCAGAGTAACTTGAGAAACCAACTGGACCTTGAGTATTGTACATTTTGCCTCG  
TGGACCCAAAGGTAGCAATCTGAAACATGAGGAGTACGATTCTACTGTTTTGTCTTCTAGGAT  
CAACTCGGTCATTACCACAGCTCAAACCTGCTTTGGGACTCCCTCCCACAAAACCTGGCTCCGG  
ATCAGGGAACACTACCAAACCAACAGCAGTCAAATCAGGTCTTTCCTTCTTTAAGTCTGATAC  
CATTAACACAGATGCTCACACTGGGGCCAGATCTGCATCTGTAAATCCTGCTGCAGGAATGA  
CACCTGGTACCCAGACCCACCCATTGACCCTGGGAGGGTTGAATGTACAACAGCAACTGCACC  
CACATGTGTTACCAATTTTTGTGCACAACTTGGAGCCCAGGGCACTATCCTAAGCTCAGAGG  
AATTGCCACAAATCTTCACGAGCCTCATCATCCATTCCCTTGTTCCCGGGAGGCATCCTGCCCCA  
CCAGTCAGGCAGGGGCTAATCCAGATGTCCAGGATGGAAGCCTTCCAGCAGGAGGAGCAGGTG  
TAAATCCTGCCACCCAGGGAACCCAGCAGGCCGCCTCCCAACTCCCAGTGGCACAGATGACG  
ACTTTGCAGTGACCACCCCTGCAGGCATCCAAAGGAGCACACATGCCATCGAGGAAGCCACCA  
CAGAATCAGCAAATGGAATTCAGTAAGCTGTTTCAAATTTTTTCAACTAAGCTGCCTCGAATT  
TGGTGATACATGTGAATCTTTATCATTGATTATATTATGGAATAGATTGAGACACATTGGATA  
GTCTTAGAAGAAATTAATTCTTAATTTACCTGAAAATATTCTTGAAATTTAGAAAATATGTT  
CTATGTAGAGAATCCCAACTTTTAAAAACAATAATTCAATGGATAAATCTGTCTTTGAAATAT  
AACATTATGCTGCCTGGATGATATGCATATTTAAACATATTTGGAAAACCTGGAAAAAAAAAAAA  
AA

97/168

**FIGURE 97**

GCTCAAGTGCCCTGCCTTGCCCCACCCAGCCCAGCCTGGCCAGAGCCCCCTGGAGAAGGAGCT  
CTCTTCTTGCTTGGCAGCTGGACCAAGGGAGCCAGTCTTGGGCGCTGGAGGGCCTGTCTTGAC  
CATGGTCCCTGCCTGGCTGTGGCTGCTTTGTGTCTCCGTCCCCCAGGCTCTCCCCAAGGCCCA  
GCCTGCAGAGCTGTCTGTGGAAGTTCCAGAAAACCTATGGTGGAAATTTCCCTTTTATACCTGAC  
CAAGTTGCCGCTGCCCCGTGAGGGGGGCTGAAGGGCCAGATCGTGCTGTGAGGGGACTCAGGCAA  
GGCAACTGAGGGGCCATTTGCTATGGATCCAGATTCTGGCTTCCTGCTGGTGACCAGGGCCCT  
GGACCGAGAGGAGCAGGCAGAGTACCAGCTACAGGTCACCCCTGGAGATGCAGGATGGACATGT  
CTTGTGGGGTCCACAGCCTGTGCTTGTGCACGTGAAGGATGAGAATGACCAGGTGCCCCATTT  
CTCTCAAGCCATCTACAGAGCTCGGCTGAGCCGGGGTACCAGGCCTGGCATCCCCTTCCTCTT  
CTTGAGGGCTTCAGACCGGGATGAGCCAGGCACAGCCAACTCGGATCTTCGATTCCACATCCT  
GAGCCAGGCTCCAGCCCAGCCTTCCCCAGACATGTTCCAGCTGGAGCCTCGGCTGGGGGCTCT  
GGCCCTCAGCCCCAAGGGGAGCACCAGCCTTGACCACGCCCTGGAGAGGACCTACCAGCTGTT  
GGTACAGGTCAAGGACATGGGTGACCAGGCCTCAGGCCACCAGGCCACTGCCACCGTGGAAGT  
CTCCATCATAGAGAGCACCTGGGTGTCCCTAGAGCCTATCCACCTGGCAGAGAATCTCAAAGT  
CCTATACCCGCACCACATGGCCCAGGTACACTGGAGTGGGGGTGATGTGCACTATCACCTGGA  
GAGCCATCCCCCGGGACCCTTTGAAGTGAATGCAGAGGGAAACCTCTACGTGACCAGAGAGCT  
GGACAGAGAAGCCCAGGCTGAGTACCTGCTCCAGGTGCGGGGCTCAGAATTTCCATGGCGAGGA  
CTATGCGGGCCCCCTCTGGAGCTGCACGTGCTGGTGATGGATGAGAATGACAACGTGCCTATCTG  
CCCTCCCCGTGACCCACAGTCAGCATCCCTGAGCTCAGTCCACCAGGTACTGAAGTGACTAG  
ACTGTCAGCAGAGGATGCAGATGCCCCCGGCTCCCCCAATTCCACGTTGTGTATCAGCTCCT  
GAGCCCTGAGCCTGAGGATGGGGTAGAGGGGAGAGCCTTCCAGGTGGACCCCACTTCAGGCAG  
TGTGACGCTGGGGGTGCTCCCACTCCGAGCAGGCCAGAACATCCTGCTTCTGGTGCTGGCCAT  
GGACCTGGCAGGCGCAGAGGGTGGCTTCAGCAGCACGTGTGAAGTCGAAGTCGCAGTCACAGA  
TATCAATGATCACGCCCTGAGTTCATCACTTCCCAGATTGGGCCTATAAGCCTCCCTGAGGA  
TGTGGAGCCCGGGACTCTGGTGGCCATGCTAACAGCCATTGATGCTGACCTCGAGCCCGCCTT  
CCGCCTCATGGATTTTGCCATTGAGAGGGGAGACACAGAAGGGACTTTTGGCCTGGATTGGGA  
GCCAGACTCTGGGCATGTTAGACTCAGACTCTGCAAGAACCTCAGTTATGAGGCAGCTCCAAG  
TCATGAGGTGGTGGTGGTGGTGCAGAGTGTGGCGAAGCTGGTGGGGCCAGGCCCAGGCCCTGG  
AGCCACCGCCACGGTGACTGTGCTAGTGGAGAGAGTGATGCCACCCCCCAAGTTGGACCAGGA  
GAGCTACGAGGCCAGTGTCCTCCATCAGTGCCCCAGCCGGCTCTTTCCTGCTGACCATCCAGCC  
CTCCGACCCCATCAGCCGAACCCTCAGGTTCTCCCTAGTCAATGACTCAGAGGGCTGGCTCTG  
CATTGAGAAATTCTCCGGGGAGGTGCACACCGCCAGTCCCTGCAGGGCGCCCAGCCTGGGGA  
CACCTACACGGTGCTTGTGGAGGCCCAGGATACAGCCCTGACTCTTGCCCCCTGTGCCCTCCCA  
ATACCTCTGCACACCCCGCCAAGACCATGGCTTGATCGTGAGTGGACCCAGCAAGGACCCCGA  
TCTGGCCAGTGGGCACGGTCCCTACAGCTTCACCCTTGGTCCCAACCCCAAGGTGCAACGGGA  
TTGGCGCCTCCAGACTCTCAATGGTTCCCATGCCTACCTCACCTTGGCCCTGCATTGGGTGGA  
GCCACGTGAACACATAATCCCCGTGGTGGTCAGCCACAATGCCCAGATGTGGCAGCTCCTGGT  
TCGAGTGATCGTGTGTCGCTGCAACGTGGAGGGGAGTGATGCGCAAGGTGGGCCGCATGAA  
GGGCATGCCACGAAGCTGTGCGCAGTGGGCATCCTTGTAGGCACCCTGGTAGCAATAGGAAT  
CTTCCTCATCCTCATTTTACCCACTGGACCATGTCAAGGAAGAAGGACCCGGATCAACCAGC  
AGACAGCGTGCCCCCTGAAGGCGACTGTCTGAATGGCCCAGGCAGCTCTAGCTGGGAGCTTGGC  
CTCTGGCTCCATCTGAGTCCCCTGGGAGAGAGCCAGCACCCAAGATCCAGCAGGGGACAGGA  
CAGAGTAGAAGCCCCTCCATCTGCCCTGGGGTGGAGGCACCATCACCATCACCAGGCATGTCT  
GCAGAGCCTGGACACCAACTTTATGGACTGCCCATGGGAGTGCTCCAAATGTCAGGGTGTGTTG  
CCCAATAATAAAGCCCCAGAGAACTGGGCTGGGCCCTATGGGAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAG

99/168

**FIGURE 99**

GGCTGACCGTGCTACATTGCCTGGAGGAAGCCTAAGGAACCCAGGCATCCAGCTGCCCCACGCC  
TGAGTCCAAGATTCTTCCCAGGAACACAAACGTAGGAGACCCACGCTCCTGGAAGCACCAGCC  
TTTATCTCTTCACCTTCAAGTCCCCTTTCTCAAGAATCCTCTGTTCTTTGCCCTCTAAAGTCT  
TGGTACATCTAGGACCCAGGCATCTTGCTTTCCAGCCACAAAGAGACAGATGAAGATGCAGAA  
AGGAAATGTTCTCCTTATGTTTGGTCTACTATTGCATTTAGAAGCTGCAACAAATTCCAATGA  
GACTAGCACCTCTGCCAACACTGGATCCAGTGTGATCTCCAGTGGAGCCAGCACAGCCACCAA  
CTCTGGGTCCAGTGTGACCTCCAGTGGGGTCAGCACAGCCACCATCTCAGGGTCCAGCGTGAC  
CTCCAATGGGGTCAGCATAGTCACCAACTCTGAGTTCCATACAACCTCCAGTGGGATCAGCAC  
AGCCACCAACTCTGAGTTCAGCACAGCGTCCAGTGGGATCAGCATAGCCACCAACTCTGAGTC  
CAGCACAACTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTCCAGCACACCCTCCAGTGG  
GGCCAGCACAGTCACCAACTCTGGGTCCAGTGTGACCTCCAGTGGAGCCAGCACTGCCACCAA  
CTCTGAGTCCAGCACAGTGTCCAGTAGGGCCAGCACTGCCACCAACTCTGAGTCTAGCACACT  
CTCCAGTGGGGCCAGCACAGCCACCAACTCTGACTCCAGCACAACTCCAGTGGGGCTAGCAC  
AGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTC  
CAGCACAGTGTCCAGTAGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACAACTCCAGTGG  
GGCCAGCACAGTCACCAACTCTGAGTCCAGAACGACCTCCAATGGGGCTGGCACAGCCACCAA  
CTCTGAGTCCAGCACAGCTCCAGTGGGGCCAGCACAGCCACCAACTCTGACTCCAGCACAGT  
GTCCAGTGGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACGACCTCCAGTGGGGCCAGCAC  
AGCCACCAACTCTGAGTCCAGCACGACCTCCAGTGGGGCTAGCACAGCCACCAACTCTGACTC  
CAGCACAACTCCAGTGGGGCCGGCACAGCCACCAACTCTGAGTCCAGCACAGTGTCCAGTGG  
GATCAGCACAGTCACCAATTCTGAGTCCAGCACACCCTCCAGTGGGGCCAACACAGCCACCAA  
CTCTGAGTCCAGTACGACCTCCAGTGGGGCCAACACAGCCACCAACTCTGAGTCCAGCACAGT  
GTCCAGTGGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGTCAGCAC  
AGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGCTAGCACAGCCACCAACTCTGACTC  
CAGCACAACTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTCTAGCACAGTGTCCAGTGG  
GATCAGCACAGTCACCAATTCTGAGTCCAGCACAACTCCAGTGGGGCCAACACAGCCACCAA  
CTCTGGGTCCAGTGTGACCTCTGCAGGCTCTGGAACAGCAGCTCTGACTGGAATGCACACAAC  
TTCCCATAGTGCATCTACTGCAGTGAAGTGAAGGCAAAGCCTGGTGGGTCCCTGGTGGCGTGGGA  
AATCTTCCTCATCACCTGGTCTCGGTTGTGGCGGCGTGGGGCTCTTTGCTGGGCTCTTCTT  
CTGTGTGAGAAACAGCCTGTCCCTGAGAAACACCTTTAACACAGCTGTCTACCACCTCATGG  
CCTCAACCATGGCCTTGGTCCAGGCCCTGGAGGGAATCATGGAGCCCCCACAGGCCAGGTG  
GAGTCCTAACTGGTTCTGGAGGAGACCAGTATCATCGATAGCCATGGAGATGAGCGGGAGGAA  
CAGCGGGCCCTGAGCAGCCCCGGAAGCAAGTGCCGCATTCTTCAGGAAGGAAGAGACCTGGGC  
ACCAAGACCTGGTTTCTTTTATTTCATCCCAGGAGACCCCTCCAGCTTTGTTTGAGATCCT  
GAAAATCTTGAAGAAGGTATTCCTCACCTTTCTTGCCTTTACCAGACACTGGAAAGAGAATAC  
TATATTGCTCATTTAGCTAAGAAATAAATACATCTCATCTAACACACACGACAAAGAGAAGCT  
GTGCTTGCCCCGGGGTGGGTATCTAGCTCTGAGATGAACTCAGTTATAGGAGAAAACCTCCAT  
GCTGGACTCCATCTGGCATTCAAAATCTCCACAGTAAAATCCAAAGACCTCAAAAAAAAAAAAA  
AA

101/168

**FIGURE 101**

GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGGAGGTTGTGACCCC  
TACGGAGCCCCAGCTTGCCACGCACCCCACTCGGCGTCGCGCGGCGTGCCCTGCTTGTCA  
GGTGGGAGGCTGGAACATCAGGCTGAAAAACAGAGTGGGTACTCTCTTCTGGGAAGCTGGCA  
ACAAATGGATGATGTGATATATGCATTCCAGGGGAAGGGAAATTGTGGTGCTTCTGAACCCAT  
GGTCAATTAACGAGGCAGTTTCTAGCTACTGCACGTACTTCATAAAGCAGGACTCTAAAAGCT  
TTGGAATCATGGTGTGTCATGGAAAGGGATTTACTTTATACTGACTCTGTTTTGGGGAAGCTTTT  
TTGGAAGCATTTTTCATGCTGAGTCCCTTTTTACCTTTGATGTTTGTAACCCATCTTGGTATC  
GCTGGATCAACAACCGCCTTGTGGCAACATGGCTCACCCCTACCTGTGGCATTATTGGAGACCA  
TGTTTGGTGTAAGTGAATTATACTGGGGATGCATTTGTTCCCTGGAGAAAGAAGTGTCATTA  
TCATGAACCATCGGACAAGAATGGACTGGATGTTCCCTGTGGAATTGCCTGATGCGATATAGCT  
ACCTCAGATTGGAGAAAATTTGCCTCAAAGCGAGTCTCAAAGGTGTTCCCTGGATTGTGGTTGGG  
CCATGCAGGCTGCTGCCTATATCTTCATTCATAGGAAATGGAAGGATGACAAGAGCCATTTTCG  
AAGACATGATTGATTACTTTTGTGATATTCACGAACCACTTCAACTCCTCATATTCCCAGAAG  
GGACTGATCTCACAGAAAACAGCAAGTCTCGAAGTAATGCATTTGCTGAAAAAATGGACTTC  
AGAAATATGAATATGTTTTACATCCAAGAACTACAGGCTTTACTTTTGTGGTAGACCGTCTAA  
GAGAAGGTAAGAACCTTGATGCTGTCCATGATATCACTGTGGCGTATCCTCACAAACATTCCTC  
AATCAGAGAAGCACCTCCTCCAAGGAGACTTTCCAGGGAAATCCACTTTACGTCCACCGGT  
ATCCAATAGACACCTCCCCACATCCAAGGAGGACCTTCAACTCTGGTGCCACAAACGGTGGG  
AAGAGAAAGAAGAGAGGCTGCGTTCCTTCTATCAAGGGGAGAAGAATTTTTATTTTACCGGAC  
AGAGTGTGATTCACCTTGCAAGTCTGAACTCAGGGTCCTTGTGGTCAAATTGCTCTCTATAC  
TGTATTGGACCCTGTTTACGCCCTGCAATGTGCCTACTCATATATTTGTACAGTCTTGTTAAGT  
GGTATTTTATAATCACCATTGTAATCTTTGTGCTGCAAGAGAGAATATTTGGTGGACTGGAGA  
TCATAGAACTTGCATGTTACCGACTTTTACACAAACAGCCACATTTAAATTCAAAGAAAAATG  
AGTAAGATTATAAGGTTTGCCATGTGAAAACCTAGAGCATATTTTGGAAATGTTCTAAACCTT  
TCTAAGCTCAGATGCATTTTGTGATGACTATGTGCAATATTTCTTACTGCCATCATTATTTGT  
TAAAGATATTTTGCACCTTAATTTTGTGGGAAAAATATTGCTACAATTTTTTTTAAATCTCTGAA  
TGTAATTTGATACTGTGTACATAGCAGGGAGTGATCGGGGTGAAATAACTTGGGCCAGAATA  
TTATTAAACAATCATCAGGCTTTTAAA

103/168

**FIGURE 103**

CGGCTCGAGCGGCTCGAGTGAAGAGCCTCTCCACGGCTCCTGCGCCTGAGACAGCTGGCCTGA  
CCTCCAAATCATCCATCCACCCCTGCTGTCATCTGTTTTTCATAGTGTGAGATCAACCCACAGG  
AATATCCATGGCTTTTTGTGCTCATTTTGGTTCTCAGTTTCTACGAGCTGGTGTGAGGACAGTG  
GCAAGTCACTGGACCGGGCAAGTTTGTCCAGGCCTTGGTGGGGGAGGACGCCGTGTTCTCCTG  
CTCCCTCTTTCCTGAGACCAGTGCAGAGGCTATGGAAGTGCGGTTCCTTCAGGAATCAGTTCCA  
TGCTGTGGTCCACCTCTACAGAGATGGGGAAGACTGGGAATCTAAGCAGATGCCACAGTATCG  
AGGGAGAACTGAGTTTGTGAAGGACTCCATTGCAGGGGGGCGTGTCTCTCTAAGGCTAAAAA  
CATCACTCCCTCGGACATCGGCCTGTATGGGTGCTGGTTCAGTTCCCAGATTTACGATGAGGA  
GGCCACCTGGGAGCTGCGGGTGGCAGCACTGGGCTCACTTCCTCTCATTTCATCGTGGGATA  
TGTTGACGGAGGTATCCAGTTACTCTGCCTGTCCTCAGGCTGGTTCCTCCAGCCACAGCCAA  
GTGGAAAGGTCCACAAGGACAGGATTTGTCTTCAGACTCCAGAGCAAATGCAGATGGGTACAG  
CCTGTATGATGTGGAGATCTCCATTATAGTCCAGGAAAATGCTGGGAGCATATTGTGTTCCAT  
CCACCTTGCTGAGCAGAGTCATGAGGTGGAATCCAAGGTATTGATAGGAGAGACGTTTTTCCA  
GCCCTCACCTTGGCGCCTGGCTTCTATTTTACTCGGGTACTCTGTGGTGCCCTGTGTGGTGT  
TGTCATGGGGATGATAATTGTTTTCTTCAAATCCAAAGGGAAAATCCAGGCGGAAGTGGACTG  
GAGAAGAAAGCACGGACAGGCAGAATTGAGAGACGCCGGGAAACACGCAGTGGAGGTGACTCT  
GGATCCAGAGACGGCTCACCCGAAGCTCTGCGTTTCTGATCTGAAAACGTAAACCCATAGAAA  
AGCTCCCCAGGAGGTGCCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCA  
GGGTTTCCAAGCAGGGAGACATTACTGGGAGGTGGACGTGGGACAAAATGTAGGGTGGTATGT  
GGGAGTGTGTGCGGATGACGTAGACAGGGGGAAGAACAATGTGACTTTGTCTCCCAACAATGG  
GTATTGGGTCCTCAGACTGACAACAGAACATTTGTATTTACATTCAATCCCCATTTTATCAG  
CCTCCCCCCCCAGCACCCCTCCTACACGAGTAGGGGTCTTCTGGACTATGAGGGTGGGACCAT  
CTCCTTCTTCAATACAAATGACCAGTCCCTTATTTATACCCTGCTGACATGTCAGTTTGAAGG  
CTTGTTGAGACCCTATATCCAGCATGCGATGTATGACGAGGAAAAGGGGACTCCCATATTCAT  
ATGTCCAGTGTCTTGGGGATTGAGACAGAGAAGACCCTGCTTAAAGGGCCCCACACCACAGACC  
CAGACACAGCCAAGGGAGAGTGTCTCCCGACAGGTGGCCCCAGCTTCCTCTCCGGAGCCTGCGC  
ACAGAGAGTCACGCCCCCACTCTCCTTTAGGGAGCTGAGGTTCTTCTGCCCTGAGCCCTGCA  
GCAGCGGCAGTCACAGCTTCCAGATGAGGGGGGATTGGCCTGACCCTGTGGGAGTCAGAAGCC  
ATGGCTGCCCTGAAGTGGGGACGGAATAGACTCACATTAGGTTTAGTTTGTGAAAACCTCCATC  
CAGCTAAGCGATCTTGAACAAGTCACAACCTCCAGGCTCCTCATTTGCTAGTCACGGACAGT  
GATTCCTGCCTCACAGGTGAAGATTAAAGAGACAACGAATGTGAATCATGCTTGCAGGTTTGA  
GGGCACAGTGTGTTGCTAATGATGTGTTTTTATATTATACATTTTCCCACCATAAACTCTGTTT  
GCTTATTCCACATTAATTTACTTTTCTATACCAAATCACCCATGGAATAGTTATTGAACAC  
CTGCTTTGTGAGGCTCAAAGAATAAAGAGGAGGTAGGATTTTTCAGTATTCTATAAGCCCAG  
CATTACCTGATACCAAAACCAGGCAAAGAAAACAGAAGAAGAGGAAGGAAAACCTACAGGTCCA  
TATCCCTCATTAACACAGACACAAAAATTCTAAATAAAATTTTAACAAATTAACTAAACAAT  
ATATTTAAAGATGATATATACTACTCAGTGTGGTTTGTCCCACAAATGCAGAGTTGGTTTAA  
TATTTAAATATCAACCAGTGTAAATTCAGCACATTAATAAAGTAAAAAAGAAAACCATAAAAAA  
AAAAAAA

105/168

**FIGURE 105**

CCTTCACAGGACTCTTCATTGCTGGTTGGCAATGATGTATCGGCCAGATGTGGTGAGGGCTAG  
GAAAAGAGTTTGTGGGAACCCTGGGTTATCGGCCTCGTCATCTTCATATCCCTGATTGTCTT  
GGCAGTGTGCATTGGACTCACTGTTTATTATGTGAGATATAATCAAAAGAAGACCTACAATTA  
CTATAGCACATTGTCATTTACAACCTGACAACTATATGCTGAGTTTGGCAGAGAGGCTTCTAA  
CAATTTTACAGAAATGAGCCAGAGACTTGAATCAATGGTGAAAAATGCATTTTATAAATCTCC  
ATTAAGGGAAGAATTTGTCAAGTCTCAGGTTATCAAGTTCAGTCAACAGAAGCATGGAGTGTT  
GGCTCATATGCTGTTGATTTGTAGATTTCACTCTACTGAGGATCCTGAACTGTAGATAAAAT  
TGTTCAACTTGTTTTACATGAAAAGCTGCAAGATGCTGTAGGACCCCTAAAGTAGATCCTCA  
CTCAGTTAAATTAATAAATCAACAAGACAGAAACAGACAGCTATCTAAACCATTGCTGCGG  
AACACGAAGAAGTAAACTCTAGGTCAGAGTCTCAGGATCGTTGGTGGGACAGAAGTAGAAGA  
GGGTGAATGGCCCTGGCAGGCTAGCCTGCAGTGGGATGGGAGTCATCGCTGTGGAGCAACCTT  
AATTAATGCCACATGGCTTGTGAGTGCTGCTCACTGTTTTACAACATATAAGAACCCTGCCAG  
ATGGACTGCTTCCTTTGGAGTAACAATAAAACCTTCGAAAATGAAACGGGGTCTCCGGAGAAT  
AATTGTCCATGAAAAATACAAACACCCATCACATGACTATGATATTTCTCTTGCAGAGCTTTC  
TAGCCCTGTTCCCTACACAAATGCAGTACATAGAGTTTGTCTCCCTGATGCATCCTATGAGTT  
TCAACCAGGTGATGTGATGTTTGTGACAGGATTTGGAGCACTGAAAAATGATGGTTACAGTCA  
AAATCATCTTCGACAAGCACAGGTGACTCTCATAGACGCTACAACCTTGCAATGAACCTCAAGC  
TTACAATGACGCCATAACTCCTAGAATGTTATGTGCTGGCTCCTTAGAAGGAAAAACAGATGC  
ATGCCAGGGTGACTCTGGAGGACCACTGGTTAGTTCAGATGCTAGAGATATCTGGTACCTTGC  
TGGAATAGTGAGCTGGGGAGATGAATGTGCGAAACCCAACAAGCCTGGTGTTTATACTAGAGT  
TACGGCCTTGCGGGACTGGATTACTTCAAAAACCTGGTATCTAAAGAGACAAAAGCCTCATGGAA  
CAGATAACATTTTTTTTTTGTGTTTGGGTGTGGAGGCCATTTTGTAGAGATACAGAATTGGAGA  
AGACTTGCAAAACAGCTAGATTTGACTGATCTCAATAAACTGTTTGCTTGATGCATGTATTTT  
CTTCCCAGCTCTGTTCCGCACGTAAGCATCCTGCTTCTGCCAGATCAACTCTGTCATCTGTGA  
GCAATAGTTGAACTTTATGTACATAGAGAAATAGATAATAACAATATTACATTACAGCCTGTA  
TTCATTTGTTCTCTAGAAGTTTTGTCAGAATTTTGACTTGTTGACATAAATTTGTAATGCATA  
TATACAATTTGAAGCACTCCTTTTCTTCAGTTCCTCAGCTCCTCTCATTTTCAGCAAATATCCA  
TTTTCAAGGTGCAGAACAGGAGTGAAAGAAAATATAAGAAGAAAAAATCCCCTACATTTTA  
TTGGCACAGAAAAGTATTAGGTGTTTTTCTTAGTGGAATATTAGAAATGATCATATTATTAT  
GAAAGGTCAAGCAAAGACAGCAGAATACCAATCACTTCATCATTTAGGAAGTATGGGAACATA  
GTTAAGGAAGTCCAGAAAGAAGCCAAGATATATCCTTATTTTCATTTCCAAACAACACTACTATG  
ATAAATGTGAAGAAGATTCTGTTTTTTTGTGACCTATAATAATTATACAACTTCATGCAATG  
TACTTGTTCTAAGCAAATTAAAGCAAATATTTATTTAACATTGTTACTGAGGATGTCAACATA  
TAACAATAAAATATAAATCACCCA



107/168

**FIGURE 107**

AGAGAAAGAAGCGTCTCCAGCTGAAGCCAATGCAGCCCTCCGGCTCTCCGCGAAGAAGTTCCC  
TGCCCCGATGAGCCCCCGCCGTGCGTCCCCGACTATCCCCAGGCGGGCGTGGGGCACC GGCC  
CAGCGCCGACGATCGCTGCCGTTTTT GCCCTTGGGAGTAGGATGTGGTGAAAGGATGGGGCTTC  
TCCCTTACGGGGCTCACA**ATGG**CCAGAGAAGATTCCGTGAAGTGTCTGCGCTGCCTGCTCTAC  
GCCCTCAATCTGCTCTTTTGGTTAATGTCCATCAGTGTGTTGGCAGTTTCTGCTTGGATGAGG  
GACTACCTAAATAATGTTCTCACTTTAACTGCAGAAACGAGGGTAGAGGAAGCAGTCATTTTG  
ACTTACTTTCTGTGTTTCATCCGGTCATGATTGCTGTTTGCTGTTTCTTATCATTGTGGGG  
ATGTTAGGATATTGTGGAACGGTGAAAAGAAATCTGTTGCTTCTTGCATGGTACTTTGGAAGT  
TTGCTTGTCAATTTTCTGTGTAGAACTGGCTTGTGGCGTTTGGACATATGAACAGGAACTTATG  
GTTCCAGTACAATGGTCAGATATGGTCACCTTTGAAAGCCAGGATGACAAATTATGGATTACCT  
AGATATCGGTGGCTTACTCATGCTTGGAAATTTTTTTCAGAGAGAGTTTAAGTGCTGTGGAGTA  
GTATATTTCACTGACTGGTTGGAAATGACAGAGATGGACTGGCCCCCAGATTCCTGCTGTGTT  
AGAGAATTCCCAGGATGTTCCAAACAGGCCACCAGGAAGATCTCAGTGACCTTTATCAAGAG  
GGTTGTGGGAAGAAAATGTATTCCTTTTTTGAGAGGAACCAAACAACCTGCAGGTGCTGAGGTTT  
CTGGGAATCTCCATTGGGGTGACACAAATCCTGGCCATGATTCTCACCATTACTCTGCTCTGG  
GCTCTGTATTATGATAGAAGGGAGCCTGGGACAGACCAAATGATGTCCTTGAAGAATGACAAC  
TCTCAGCACCTGTCTGTCCTCAGTAGAACTGTTGAAACCAAGCCTGTCAAGAATCTTTGAA  
CACACATCCATGGCAAACAGCTTTAATACACACTTTGAGATGGAGGAGTTA**TAAAA**AGAAATG  
TCACAGAAGAAAACCACAAACTTGTTTTATTGGACTTGTGAATTTTTGAGTACATACTATGTG  
TTTCAGAAATATGTAGAAATAAAAATGTTGCCATAAAATAACACCTAAGCATATACTATTCTA  
TGCTTTAAATGAGGATGGAAAAGTTTCATGTCTAAGTCACCACCTGGACAATAATTGATGC  
CCTTAAATGCTGAAGACAGATGTCAACCCACTGTGTAGCCTGTGTATGACTTTTACTGAAC  
ACAGTTATGTTTTGAGGCAGCATGGTTTGTATTAGCATTTCGCGCATCCATGCAAACGAGTCACA  
TATGGTGGGACTGGAGCCATAGTAAAGGTTGATTTACTTCTACCAACTAGTATATAAAGTACT  
AATTAAATGCTAACATAGGAAGTTAGAAAATACTAATAACTTTTATTACTCAGCGATCTATTC  
TTCTGATGCTAAATAAATTATATATCAGAAAACCTTTCAATATTGGTGACTACCTAAATGTGAT  
TTTTGCTGGTTACTAAAATATTCTTACCCTTAAAAGAGCAAGCTAACACATTGTCTTAAGCT  
GATCAGGGATTTTTTGTATATAAGTCTGTGTTAAATCTGTATAATTCAGTCGATTTTCAGTTCT  
GATAATGTTAAGAATAACCATTATGAAAAGGAAAATTTGTCCTGTATAGCATCATTATTTTTA  
GCCTTTCCTGTTAATAAAGCTTTACTATTCTGTCTGGCTTATATTACACATATAACTGTTA  
TTTAAATACTTAACCACTAATTTTGAAAATTACCAGTGTGATACATAGGAATCATTATTCAGA  
ATGTAGTCTGGTCTTTAGGAAGTATTAATAAGAAAATTTGCACATAACTTAGTTGATTCAGAA  
AGGACTTGATGCTGTTTTTCTCCCAAATGAAGACTCTTTTGGACACTAAACACTTTTTTAAAA  
AGCTTATCTTTGCCTTCTCCAAACAAGAAGCAATAGTCTCCAAGTCAATATAAATTCTACAGA  
AAATAGTGTTCTTTTTCTCCAGAAAAATGCTTGTGAGAATCATTAACACATGTGACAATTTAG  
AGATTCTTTGTTTTATTTCACTGATTAATATACTGTGGCAAATTACACAGATTATTAAATTTT  
TTTACAAGAGTATAGTATATTTATTTGAAATGGGAAAAGTGCATTTTACTGTATTTTGTGTAT  
TTTGTATTATTTCTCAGAATATGGAAAGAAAATTAAATGTGTCAATAAATATTTTCTAGAGAG  
TAA

109/168

**FIGURE 109**

CCAAGGCCAGAGCTGTGGACACCTTATCCCACTCATCCTCATCCTCTTCCTCTGATAAAGCCC  
CTACCAGTGCTGATAAAGTCTTTCTCGTGAGAGCCTAGAGGCCTTAAAAAAAAAAGTGCTTGA  
AAGAGAAGGGGACAAAGGAACACCAGTATTAAGAGGATTTTCCAGTGTTTCTGGCAGTTGGTC  
CAGAAGGATGCTCCTCCATTCTGCTTCTCACCTGCCTCTTCATCACAGGCACCTCCGTGTCACC  
CGTGGCCCTAGATCCTTGTCTGCTTACATCAGCCTGAATGAGCCCTGGAGGAACACTGACCA  
CCAGTTGGATGAGTCTCAAGGTCCTCCTCTATGTGACAACCATGTGAATGGGGAGTGGTACCA  
CTTCACGGGCATGGCGGGAGATGCCATGCCTACCTTCTGCATACCAGAAAACCACTGTGGAAC  
CCACGCACCTGTCTGGCTCAATGGCAGCCACCCCTAGAAAGGCGACGGCATTGTGCAACGCCA  
GGCTTGTGCCAGCTTCAATGGGAACTGCTGTCTCTGGAACACCACGGTGGAAGTCAAGGCTTG  
CCCTGGAGGCTACTATGTGTATCGTCTGACCAAGCCCAGCGTCTGCTTCCACGTCTACTGTGG  
TCATTTTATGACATCTGCGACGAGGACTGCCATGGCAGCTGCTCAGATACCAGCGAGTGCAC  
ATGCGCTCCAGGAACGTGTGCTAGGCCCTGACAGGCAGACATGCTTTGATGAAAATGAATGTGA  
GCAAAACAACGGTGGCTGCAGTGAGATCTGTGTGAACCTCAAAAACCTCCTACCGCTGTGAGTG  
TGGGGTTGGCCGTGTGCTAAGAAGTGATGGCAAGACTTGTGAAGACGTTGAAGGATGCCACAA  
TAACAATGGTGGCTGCAGCCACTCTTGCCTTGGATCTGAGAAAGGCTACCAGTGTGAATGTCC  
CCGGGGCCTGGTGTCTGTCTGAGGATAACCACACTTGCCAAGTCCCTGTGTTGTGCAAAATCAAA  
TGCCATTGAAGTGAACATCCCCAGGGAGCTGGTGGTGGCCTGGAGCTCTTCTCTCTCAAGACATGTGG  
CTCCTGCCGAGGAGTGTCCAACGGCACCCATGTCAACATCCTCTTCTCTCTCAAGACATGTGG  
TACAGTGGTTCGATGTGGTGAATGACAAGATTGTGGCCAGCAACCTCGTGACAGGTCTACCCAA  
GCAGACCCCGGGGAGCAGCGGGGACTTCATCATCCGAACCAGCAAGCTGCTGATCCCGGTGAC  
CTGCGAGTTTCCACGCCTGTACACCATTCTGAAGGATACGTTCCCAACCTTCGAAACTCCCC  
ACTGGAAATCATGAGCCGAAATCATGGGATCTTCCCATTCACTCTGGAGATCTTCAAGGACAA  
TGAGTTTGAAGAGCCTTACCGGGAAGCTCTGCCCACCCTCAAGCTTCGTGACTCCCTCTACTT  
TGGCATTGAGCCCGTGGTGCACGTGAGCGGCTTGGAAGCTTGGTGGAGAGCTGCTTTGCCAC  
CCCCACCTCCAAGATCGACGAGGTCTGAAATACTACCTCATCCGGGATGGCTGTGTTTCAGA  
TGACTCGGTAAAGCAGTACACATCCCGGGATCACCTAGCAAAGCACTTCCAGGTCCCTGTCTT  
CAAGTTTGTGGGCAAAGACCACAAGGAAGTGTCTGCACTGCCGGGTCTTGTCTGTGGAGT  
GTTGGACGAGCGTTCCCGCTGTGCCCAGGGTTGCCACCGGCGAATGCGTCGTGGGGCAGGAGG  
AGAGGACTCAGCCGGTCTACAGGGCCAGACGCTAACAGGCGGCCCCGATCCGCATCGACTGGGA  
GGACTAGTTTCGTAGCCATACCTCGAGTCCCTGCATTGGACGGCTCTGCTCTTTGGAGCTTCTC  
CCCCACCGCCCTCTAAGAACATCTGCCAACAGCTGGGTTCAGACTTCACACTGTGAGTTCAG  
ACTCCAGCACCAACTCACTCTGATTCTGGTCCATTCACTGGGCACAGGTACAGCACTGCTG  
AACAATGTGGCCTGGGTGGGGTTTCATCTTTCTAGGGTTGAAAATAAATGTCCACCCAGAA  
AGACACTCACCCCATTTCCCTCATTTCTTCTTCTACACTTAAATACCTCGTGTATGGTGAATC  
AGACCACAAAATCAGAAGCTGGGTATAATATTTCAAGTTACAAACCCTAGAAAAATTAAACAG  
TACTGAAATTATGACTTAAATACCCAATGACTCCTTAAATATGTAAATTATAGTTATACCTT  
GAAATTTCAATTCAAATGCAGACTAATTATAGGGAATTTGGAAGTGTATCAATAAACAGTAT  
ATAATTTT

111/168

**FIGURE 111**

GAGAGAGGCAGCAGCTTGCTCAGCGGACAAGGATGCTGGGCGTGAGGGACCAAGGCCTGCCCT  
GCACTCGGGCCTCCTCCAGCCAGTGCTGACCAGGGACTTCTGACCTGCTGGCCAGCCAGGACC  
TGTGTGGGGAGGCCCTCCTGCTGCCTTGGGGTGACAATCTCAGCTCCAGGCTACAGGGAGACC  
GGGAGGATCACAGAGCCAGCATGTTACAGGATCCTGACAGTGATCAACCTCTGAACAGCCTCG  
ATGTCAAACCCCTGCGCAAACCCCGTATCCCCATGGAGACCTTCAGAAAGGTGGGGATCCCCA  
TCATCATAGCACTACTGAGCCTGGCGAGTATCATCATTGTGGTTGTCCTCATCAAGGTGATTC  
TGGATAAATACTACTTCTCTGCGGGCAGCCTCTCCACTTCATCCCGAGGAAGCAGCTGTGTG  
ACGGAGAGCTGGACTGTCCCTTGGGGGAGGACGAGGAGCACTGTGTCAAGAGCTTCCCCGAAG  
GGCCTGCAGTGGCAGTCCGCCTCTCCAAGGACCGATCCACACTGCAGGTGCTGGACTCGGCCA  
CAGGGAAGTGGTTCTCTGCCTGTTTCGACAACTTCACAGAAGCTCTCGCTGAGACAGCCTGTA  
GGCAGATGGGCTACAGCAGAGCTGTGGAGATTGGCCCAGACCAGGATCTGGATGTTGTTGAAA  
TCACAGAAAACAGCCAGGAGCTTCGCATGCGGAACTCAAGTGGGCCCTGTCTCTCAGGCTCCC  
TGGTCTCCCTGCACTGTCTTGCTGTGGGAAGAGCCTGAAGACCCCCCGTGTGGTGGGTGGGG  
AGGAGGCCTCTGTGGATTCTTGGCCTTGGCAGGTCAGCATCCAGTACGACAAACAGCACGTCT  
GTGGAGGGAGCATCCTGGACCCCCACTGGGTCTCACGGCAGCCCACTGCTTCAGGAAACATA  
CCGATGTGTTCAACTGGAAGGTGCGGGCAGGCTCAGACAACTGGGCAGCTTCCCATCCCTGG  
CTGTGGCCAAGATCATCATCATTGAATTCAACCCCATGTACCCCAAAGACAATGACATCGCCC  
TCATGAAGCTGCAGTTCCCACTCACTTTCTCAGGCACAGTCAGGCCCATCTGTCTGCCCTTCT  
TTGATGAGGAGCTCACTCCAGCCACCCCACTCTGGATCATTGGATGGGGCTTTACGAAGCAGA  
ATGGAGGGAAGATGTCTGACATACTGCTGCAGGCGTCAGTCCAGGTCATTGACAGCACACGGT  
GCAATGCAGACGATGCGTACCAGGGGGGAAGTCAACGAGAAGATGATGTGTGCAGGCATCCCGG  
AAGGGGGTGTGGACACCTGCCAGGGTGACAGTGGTGGGCCCTGATGTACCAATCTGACCAGT  
GGCATGTGGTGGGCATCGTTAGCTGGGGCTATGGCTGCGGGGGCCCGAGCACCCAGGAGTAT  
ACACCAAGGTCTCAGCCTATCTCAACTGGATCTACAATGTCTGGAAGGCTGAGCTGTAATGCT  
GCTGCCCCTTTGCAGTGCTGGGAGCCGCTTCCTTCCTGCCCTGCCACCTGGGGATCCCCCA  
AGTCAGACACAGAGCAAGAGTCCCCCTGGGTACACCCCTCTGCCACAGCCTCAGCATTTCTT  
GGAGCAGCAAAGGGCCTCAATTCTGTAAGAGACCCCTCGCAGCCCAGAGGCGCCCAGAGGAAG  
TCAGCAGCCCTAGCTCGGCCACACTTGGTGCTCCAGCATCCAGGGAGAGACACAGCCCACT  
GAACAAGGTCTCAGGGGTATTGCTAAGCCAAGAAGGAACTTTCCACACTACTGAATGGAAGC  
AGGCTGTCTTGTAAGGCCAGATCACTGTGGGCTGGAGAGGAGAAGGAAAGGGTCTGCGCCA  
GCCCTGTCCGTCTTCACCCATCCCCAAGCCTACTAGAGCAAGAAACCAGTTGTAATATAAAAT  
GCACTGCCCTACTGTTGGTATGACTACCGTTACCTACTGTTGTCATTGTTATTACAGCTATGG  
CCACTATTATTAAAGAGCTGTGTAACATCTCTGGCAAAAAAAAAAAAA

113/168

**FIGURE 113**

GGCTGGACTGGAACCTCCTGGTCCCAAGTGATCCACCCGCCTCAGCCTCCCAAGGTGCTGTGAT  
TATAGGTGTAAGCCACCGTGTCTGGCCTCTGAACAACCTTTTTCAGCAACTAAAAAGCCACAG  
GAGTTGAACTGCTAGGATTCTGACTATGCTGTGGTGGCTAGTGCTCCTACTCCTACCTACATT  
AAAATCTGTTTTTTGTTCTCTTGTAAGTACCTTTACCTTCCTAACACAGAGGATCTGTCACT  
GTGGCTCTGGCCCAAACCTGACCTTCACTCTGGAACGAGAACAGAGGTTTCTACCCACACCGT  
CCCCTCGAAGCCGGGACAGCCTCACCTTGCTGGCCTCTCGCTGGAGCAGTGCCCTCACCAAC  
TGTCTCACGTCTGGAGGCACTGACTCGGGCAGTGCAGGTAGCTGAGCCTCTTGGTAGCTGCGG  
CTTTCAAGGTGGGCCTTGCCCTGGCCGTAGAAGGGATTGACAAGCCCGAAGATTTCATAGGCG  
ATGGCTCCCACTGCCCAGGCATCAGCCTTGCTGTAGTCAATCACTGCCCTGGGGCCAGGACGG  
GCCGTGGACACCTGCTCAGAAGCAGTGGGTGAGACATCACGCTGCCCGCCCATCTAACCTTTT  
CATGTCCTGCACATCACCTGATCCATGGGCTAATCTGAACTCTGTCCCAAGGAACCCAGAGCT  
TGAGTGAGCTGTGGCTCAGACCCAGAAGGGGTCTGCTTAGACCACCTGGTTTATGTGACAGGA  
CTTGCATTCTCCTGGAACATGAGGGAACGCCGGAGGAAAGCAAAGTGGCAGGGAAGGAACTTG  
TGCCAAATTATGGGTCAGAAAAGATGGAGGTGTTGGGTATCACAAGGCATCGAGTCTCCTGC  
ATTCAGTGGACATGTGGGGGAAGGGCTGCCGATGGCGCATGACACACTCGGGACTCACCTCTG  
GGGCCATCAGACAGCCGTTTCCGCCCCGATCCACGTACCAGCTGCTGAAGGGCAACTGCAGGC  
CGATGCTCTCATCAGCCAGGCAGCAGCCAAAATCTGCGATCACCAGCCAGGGGCAGCCGTCTG  
GGAAGGAGCAAGCAAAGTGACCATTTCTCCTCCCCTCCTTCCCTCTGAGAGGCCCTCCTATGT  
CCCTACTAAAGCCACCAGCAAGACATAGCTGACAGGGGCTAATGGCTCAGTGTTGGCCCAGGA  
GGTCAGCAAGGCCTGAGAGCTGATCAGAAGGGCCTGCTGTGCGAACACGGAAATGCCTCCAGT  
AAGCACAGGCTGCAAAATCCCCAGGCAAAGGACTGTGTGGCTCAATTTAAATCATGTTCTAGT  
AATTGGAGCTGTCCCCAAGACCAAAGGAGCTAGAGCTTGGTTCAAATGATCTCCAAGGGCCCT  
TATACCCCAGGAGACTTTGATTTGAATTTGAAACCCCAAATCCAAACCTAAGAACCAGGTGCA  
TTAAGAATCAGTTATTGCCGGGTGTGGTGGCCTGTAATGCCAACATTTTGGGAGGCCGAGGCG  
GGTAGATCACCTGAGGTCAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCCCTGTCTC  
TACTAAAAATACAAAAAACTAGCCAGGCATGGTGGTGTGTGCCTGTATCCCAGCTACTCGGG  
AGGCTGAGACAGGAGAATTACTTGAACCTGGGAGGTGAAGGAGGCTGAGACAGGAGAATCACT  
TCAGCCTGAGCAACACAGCGAGACTCTGTCTCAGAAAAAATAAAAAAAGAATTATGGTTATTT  
GTAA

115/168

**FIGURE 115**

CAGCAGTGGTCTCTCAGTCCTCTCAAAGCAAGGAAAGAGTACTGTGTGCTGAGAGACCATGGC  
AAAGAATCCTCCAGAGAATTGTGAAGACTGTCACATTCTAAATGCAGAAGCTTTTAAATCCAA  
GAAAATATGTAAATCACTTAAGATTTGTGGACTGGTGTGTTGGTATCCTGGCCCTAACTCTAAT  
TGTCTGTGTTTTGGGGGAGCAAGCACTTCTGGCCGGAGGTACCCAAAAAAGCCTATGACATGGA  
GCACACTTTCTACAGCAATGGAGAGAAGAAGAAGATTTACATGGAAATTGATCCTGTGACCAG  
AACTGAAATATTCAGAAGCGGAAATGGCACTGATGAAACATTGGAAGTGCACGACTTTAAAAA  
CGGATACACTGGCATCTACTTCGTGGGTCTTCAAAAATGTTTTATCAAAACTCAGATTAAAGT  
GATTCCTGAATTTTCTGAACCAGAAGAGGAAATAGATGAGAATGAAGAAATTACCACAACTTT  
CTTTGAACAGTCAGTGATTTGGGTCCCAGCAGAAAAGCCTATTGAAAACCGAGATTTTCTTAA  
AAATTCCAAAATTCTGGAGATTTGTGATAACGTGACCATGTATTGGATCAATCCCCTCTAAT  
ATCAGTTTCTGAGTTACAAGACTTTGAGGAGGAGGGAGAAGATCTTCACTTTCCTGCCAACGA  
AAAAAAGGGATTGAACAAAATGAACAGTGGGTGGTCCCTCAAGTGAAAGTAGAGAAGACCCG  
TCACGCCAGACAAGCAAGTGAGGAAGAACTTCCAATAAATGACTATACTGAAAATGGAATAGA  
ATTTGATCCCATGCTGGATGAGAGAGGTTATTGTTGTATTTACTGCCGTGCGAGGCAACCGCTA  
TTGCCGCCGCGTCTGTGAACCTTTACTAGGCTACTACCCATATCCATACTGCTACCAAGGAGG  
ACGAGTCATCTGTCGTGTCATCATGCCTTGTAAGTGGTGGGTGGCCCGCATGCTGGGGAGGGT  
CTAATAGGAGGTTTGAGCTCAAATGCTTAAACTGCTGGCAACATATAATAAATGCATGCTATT  
CAATGAATTTCTGCCTATGAGGCATCTGGCCCCTGGTAGCCAGCTCTCCAGAATTACTTGTAG  
GTAATTCCTCTCTTCATGTTCTAATAAACTTCTACATTATCACCAAAAAAAAAAAAAAAAAAAAA

117/168

**FIGURE 117**

GAGCTCCCCTCAGGAGCGCGTTAGCTTCACACCTTCGGCAGCAGGAGGGCGGCAGCTTCTCGC  
AGGCGGCAGGGCGGGCGGCCAGGATCATGTCCACCACCACATGCCAAGTGGTGGCGTTCCTCC  
TGTCCATCCTGGGGCTGGCCGGCTGCATCGCGGCCACCGGGATGGACATGTGGAGCACCCAGG  
ACCTGTACGACAACCCCGTCACCTCCGTGTTCCAGTACGAAGGGCTCTGGAGGAGCTGCGTGA  
GGCAGAGTTCAGGCTTCACCGAATGCAGGCCCTATTTACCATCCTGGGACTTCCAGCCATGC  
TGCAGGCAGTGCGAGCCCTGATGATCGTAGGCATCGTCCTGGGTGCCATTGGCCTCCTGGTAT  
CCATCTTTGCCCTGAAATGCATCCGCATTGGCAGCATGGAGGACTCTGCCAAAGCCAAACATGA  
CACTGACCTCCGGGATCATGTTCAATTGTCTCAGGTCTTTGTGCAATTGCTGGAGTGTCTGTGT  
TTGCCAACATGCTGGTGACTAACTTCTGGATGTCCACAGCTAACATGTACACCGGCATGGGTG  
GGATGGTGCAGACTGTTCAAGACCAGGTACACATTTGGTGCGGCTCTGTTTCGTGGGCTGGGTG  
CTGGAGGCCTCACACTAATTGGGGGTGTGATGATGTGCATCGCCTGCCGGGGCCTGGCACCAG  
AAGAAACCAACTACAAAGCCGTTTCTTATCATGCCTCAGGCCACAGTGTTCCTACAAGCCTG  
GAGGCTTCAAGGCCAGCACTGGCTTTGGGTCCAACACCAAAAACAAGAAGATATACGATGGAG  
GTGCCCCGCACAGAGGACGAGGTACAATCTTATCCTTCCAAGCACGACTATGTGTAATGCTCTA  
AGACCTCTCAGCACGGGCGGAAGAACTCCCGGAGAGCTCACCCAAAAACAAGGAGATCCCA  
TCTAGATTTCTTCTTGCTTTTGACTCACAGCTGGAAGTTAGAAAAGCCTCGATTTTCATCTTG  
GAGAGGCCAAATGGTCTTAGCCTCAGTCTCTGTCTCTAAATATTCCACCATAAAACAGCTGAG  
TTATTTATGAATTAGAGGCTATAGCTCACATTTTCAATCCTCTATTTCTTTTTTTAAATATAA  
CTTTCTACTCTGATGAGAGAATGTGGTTTTAATCTCTCTCTCACATTTTGATGATTTAGACAG  
ACTCCCCCTCTTCCTCCTAGTCAATAAACCCATTGATGATCTATTTCCCAGCTTATCCCCAAG  
AAAACTTTTGAAAGGAAAGAGTAGACCCAAAGATGTTATTTTCTGCTGTTTGAATTTTGTCTC  
CCCACCCCCAACTTGGCTAGTAATAAACTTACTGAAGAAGAAGCAATAAGAGAAAGATATT  
TGTAATCTCTCAGCCCATGATCTCGGTTTTCTTACACTGTGATCTTAAAAGTTACCAAACCA  
AAGTCATTTTCAGTTTGAGGCAACCAAACCTTTCTACTGCTGTTGACATCTTCTTATTACAGC  
AACACCATTCTAGGAGTTTCCTGAGCTCTCCACTGGAGTCCTCTTCTGTGCGGGTCAGAAA  
TTGTCCCTAGATGAATGAGAAAATTATTTTTTTTTAATTTAAGTCCTAAATATAGTTAAAATAA  
ATAATGTTTTAGTAAATGATACACTATCTCTGTGAAATAGCCTCACCCCTACATGTGGATAG  
AAGGAAATGAAAAATAATTGCTTTGACATTGTCTATATGGTACTTTGTAAAGTCATGCTTAA  
GTACAAATTCCATGAAAAGCTCACACCTGTAATCCTAGCACTTTGGGAGGCTGAGGAGGAAGG  
ATCACTTGAGCCCAGAAGTTCGAGACTAGCCTGGGCAACATGGAGAAGCCCTGTCTCTACAAA  
ATACAGAGAGAAAAAATCAGCCAGTCATGGTGGCATAACCTGTAGTCCCAGCATTCCGGGAG  
GCTGAGGTGGGAGGATCACTTGAGCCCAGGGAGGTTGGGGCTGCAGTGAGCCATGATCACACC  
ACTGCACTCCAGCCAGGTGACATAGCGAGATCCTGTCTAAAAAAATAAAAAATAAATAATGGA  
ACACAGCAAGTCCTAGGAAGTAGGTTAAACTAATTCTTTAA

119/168

**FIGURE 119**

GGAAAACTGTTCTCTTCTGTGGCACAGAGAACCCTGCTTCAAAGCAGAAGTAGCAGTTCCGG  
AGTCCAGCTGGCTAAAACTCATCCCAGAGGATAATGGCAACCCATGCCTTAGAAATCGCTGGG  
CTGTTTCTTGGTGGTGGTGGGAATGGTGGGCACAGTGGCTGTCACTGTGCCTCAGTGGAGA  
GTGTCGGCCTTCATTGAAAACAACATCGTGGTTTTTGAAAACCTCTGGGAAGGACTGTGGATG  
AATTGCGTGAGGCAGGCTAACATCAGGATGCAGTGCAAAATCTATGATTCCCTGCTGGCTCTT  
TCTCCGGACCTACAGGCAGCCAGAGGACTGATGTGTGCTGCTTCCGTGATGTCCTTCTTGGCT  
TTCATGATGGCCATCCTTGGCATGAAATGCACCAGGTGCACGGGGGACAATGAGAAGGTGAAG  
GCTCACATTCTGCTGACGGCTGGAATCATCTTCATCATCACGGGCATGGTGGTGTCTCATCCCT  
GTGAGCTGGGTTGCCAATGCCATCATCAGAGATTTCTATAACTCAATAGTGAATGTTGCCCAA  
AAACGTGAGCTTGGAGAAGCTCTCTACTTAGGATGGACCACGGCACTGGTGTCTGATTGTTGGA  
GGAGCTCTGTTCTGCTGCGTTTTTTGTTGCAACGAAAAGAGCAGTAGCTACAGATACTCGATA  
CCTTCCCATCGCACAAACCCAAAAAAGTTATCACACCGGAAAGAAGTCACCGAGCGTCTACTCC  
AGAAGTCAGTATGTGTAGTTGTGTATGTTTTTTTAACTTTACTATAAAGCCATGCAAATGACA  
AAAATCTATATTACTTTCTCAAATGGACCCCAAAGAACTTTGATTTACTGTTCTTAACTGC  
CTAATCTTAATTACAGGAAGTGTGCATCAGCTATTTATGATTCTATAAGCTATTTTCAGCAGAA  
TGAGATATTAAACCCAATGCTTTGATTGTTCTAGAAAGTATAGTAATTTGTTTTCTAAGGTGG  
TTCAAGCATCTACTCTTTTTATCATTTACTTTCAAATGACATTGCTAAAGACTGCATTATTTT  
ACTACTGTAATTTCTCCACGACATAGCATTATGTACATAGATGAGTGTAAACATTTATATCTCA  
CATAGAGACATGCTTATATGGTTTTATTTAAAATGAAATGCCAGTCCATTACACTGAATAAAT  
AGAACTCAACTATTGCTTTTTCAGGGAAATCATGGATAGGGTTGAAGAAGGTACTATTAATTG  
TTTAAAAACAGCTTAGGGATTAATGTCCTCCATTTATAATGAAGATTAAAATGAAGGCTTTAA  
TCAGCATTGTAAAGGAAATTGAATGGCTTTCTGATATGCTGTTTTTTAGCCTAGGAGTTAGAA  
ATCCTAACTTCTTTATCCTCTTCTCCCAGAGGCTTTTTTTTTCTTGTGTATTAAATTAACATT  
TTTAAAACGCAGATATTTTGTCAAGGGGCTTTGCATTCAAACCTGCTTTTCCAGGGCTATACTC  
AGAAGAAAGATAAAAGTGTGATCTAAGAAAAAGTGATGGTTTTAGGAAAGTGAAAATATTTTT  
GTTTTTGTATTTGAAGAAGAATGATGCATTTTGACAAGAAATCATATATGTATGGATATATTT  
TAATAAGTATTTGAGTACAGACTTTGAGGTTTCATCAATATAAATAAAAGAGCAGAAAAATAT  
GTCTTGGTTTTCATTTGCTTACCAAAAAACAACAACAAAAAAGTTGTCCTTTGAGAAGTTT  
ACCTGCTCCTATGTGGGTACCTGAGTCAAAATTGTCATTTTTGTTCTGTGAAAAATAAATTTT  
CTTCTTGTACCATTTCTGTTTAGTTTTACTAAAATCTGTAAATACTGTATTTTTCTGTTTATT  
CCAAATTTGATGAACTGACAATCCAATTTGAAAGTTTGTGTGCGACGTCTGTCTAGCTTAAAT  
GAATGTGTTCTATTTGCTTTTATACATTTATATTAATAAATTGTACATTTTTCTAATT

121/168

**FIGURE 121**

GGAGAGAGGCGCGCGGGTGAAAGGCGCATTGATGCAGCCTGCGGCGGCCTCGGAGCGCGGCGG  
AGCCAGACGCTGACCACGTTCCCTCTCCTCGGTCTCCTCCGCCTCCAGCTCCGCGCTGCCCCGGC  
AGCCGGGAGCCATGCGACCCCAGGGCCCCGCGCCTCCCCGCAGCGGCTCCGCGGCCTCCTGC  
TGCTCCTGCTGCTGCAGCTGCCCCGCGCCGTCGAGCGCCTCTGAGATCCCCAAGGGGAAGCAAA  
AGGCGCAGCTCCGGCAGAGGGAGGTGGTGGACCTGTATAATGGAATGTGCTTACAAGGGCCAG  
CAGGAGTGCCTGGTTCGAGACGGGAGCCCTGGGGCCAATGTTATTCCGGGTACACCTGGGATCC  
CAGGTCGGGATGGATTCAAAGGAGAAAAGGGGGAATGTCTGAGGGAAAGCTTTGAGGAGTCCT  
GGACACCCAACTACAAGCAGTGTTTCATGGAGTTCATTGAATTATGGCATAGATCTTGGGAAAA  
TTGCGGAGTGATACATTTACAAAGATGCGTTCAAATAGTGCTCTAAGAGTTTTGTTTCAGTGGCT  
CACTTCGGCTAAAATGCAGAAATGCATGCTGTCAGCGTTGGTATTTACATTCAATGGAGCTG  
AATGTTTCAGGACCTCTTCCCATTGAAGCTATAATTTATTTGGACCAAGGAAGCCCTGAAATGA  
ATTCAACAATTAATATTCATCGCACTTCTTCTGTGGAAGGACTTTGTGAAGGAATTGGTGCTG  
GATTAGTGGATGTTGCTATCTGGGTGGCACTTGTTTCAGATTACCCAAAAGGAGATGCTTCTA  
CTGGATGGAATTCAGTTTCTCGCATCATTATTGAAGAACTACCAAAATAAATGCTTTAATTTT  
CATTTGCTACCTCTTTTTTTTATTATGCCTTGGAATGGTTCACTTAAATGACATTTTAAATAAG  
TTTATGTATACATCTGAATGAAAAGCAAAGCTAAATATGTTTACAGACCAAAGTGTGATTTCA  
CACTGTTTTTAAATCTAGCATTATTCATTTTGCTTCAATCAAAGTGGTTTCAATATTTTTTT  
TAGTTGGTTAGAATACTTTCTTCATAGTCACATTCTCTCAACCTATAATTTGGAATATTGTTG  
TGGTCTTTTGTTTTTTCTCTTAGTATAGCATTTTTTAAAAAATATAAAAGCTACCAATCTTTG  
TACAATTTGTAAATGTTAAGAATTTTTTTTATATCTGTAAATAAAAATTATTTCCAACA



123/168

**FIGURE 123**

GCTGAGCGTGTGCGCGGTACGGGGCTCTCCTGCCTTCTGGGCTCCAACGCAGCTCTGTGGCTG  
AACTGGGTGCTCATCACGGGAAGTGTGGGCTATGGAATACAGATGTGGCAGCTCAGGTAGCC  
CCAAATTGCCTGGAAGAATACATCATGTTTTTCGATAAGAAGAAATTGTAGGATCCAGTTTTT  
TTTTTAACCGCCCCCTCCCCACCCCCCAAAAAAAGTGTAAAGATGCAAAAACGTAATATCCAT  
GAAGATCCTATTACCTAGGAAGATTTTGATGTTTTGCTGCGAATGCGGTGTTGGGATTTATTT  
GTTCTTGGAGTGTTCGCGTGGCTGGCAAAGAATAATGTTCCAAAATCGGTCCATCTCCCAAG  
GGGTCCAATTTTTCTTCCTGGGTGTCAGCGAGCCCTGACTCACTACAGTGCAGCTGACAGGGG  
CTGTCATGCAACTGGCCCCCTAAGCCAAAGCAAAGACCTAAGGACGACCTTTGAACAATAACAA  
AGGATGGGTTTCAATGTAATTAGGCTACTGAGCGGATCAGCTGTAGCACTGGTTATAGCCCCC  
ACTGTCTTACTGACAATGCTTTCTTCTGCCGAACGAGGATGCCCTAAGGGCTGTAGGTGTGAA  
GGCAAAATGGTATATTGTGAATCTCAGAAATTACAGGAGATACCCTCAAGTATATCTGCTGGT  
TGCTTAGGTTTGTCCCTTCGCTATAACAGCCTTCAAAAAGTAAAGTATAATCAATTTAAAGGG  
CTCAACCAGCTCACCTGGCTATACCTTGACCATAACCATATCAGCAATATTGACGAAAATGCT  
TTTAATGGAATACGCAGACTCAAAGAGCTGATTCTTAGTTCCAATAGAATCTCCTATTTTCTT  
AACAATACCTTCAGACCTGTGACAAATTTACGGAAGCTGGATCTGTCTTATAATCAGCTGCAT  
TCTCTGGGATCTGAACAGTTTCGGGGCTTGCGGAAGCTGCTGAGTTTACATTTACGGTCTAAC  
TCCCTGAGAACCATCCCTGTGCGAATATTCCAAGACTGCCGCAACCTGGAAGCTTTTGACCTG  
GGATATAACCGGATCCGAAGTTTAGCCAGGAATGTCTTTGCTGGCATGATCAGACTCAAAGAA  
CTTCACCTGGAGCACAATCAATTTTCCAAGCTCAACCTGGCCCTTTTTCCAAGGTTGGTCAGC  
CTTCAGAACCTTTACTTGCAAGTGAATAAAATCAGTGTATAGGACAGACCATGTCTTGACCTG  
TGGAGCTCCTTACAAAGGCTTGATTTATCAGGCAATGAGATCGAAGCTTTCAGTGGACCCAGT  
GTTTTCCAGTGTGTCCCGAATCTGCAGCGCTCAACCTGGATTCCAACAAGCTCACATTTATT  
GGTCAAGAGATTTTGGATTCTTGATATCCCTCAATGACATCAGTCTTGCTGGGAATATATGG  
GAATGCAGCAGAAATATTTGCTCCCTTGTAAGTGGCTGAAAAGTTTTAAAGGTCTAAGGGAG  
AATACAATTATCTGTGCCAGTCCCAAAGAGCTGCAAGGAGTAAATGTGATCGATGCAGTGAAG  
AACTACAGCATCTGTGGCAAAAGTACTACAGAGAGGTTTGATCTGGCCAGGGCTCTCCCAAAG  
CCGACGTTTAAGCCCAAGCTCCCCAGGCCGAAGCATGAGAGCAAACCCCTTTGCCCCCGACG  
GTGGGAGCCACAGAGCCCGGCCAGAGACCGATGCTGACGCCGAGCACATCTCTTCCATAAA  
ATCATCGCGGGCAGCGTGGCGCTTTTCCTGTCCGTGCTCGTCATCCTGCTGGTTATCTACGTG  
TCATGGAAGCGGTACCCTGCGAGCATGAAGCAGCTGCAGCAGCGCTCCCTCATGCGAAGGCAC  
AGGAAAAAGAAAAGACAGTCCCTAAAGCAAATGACTCCAGCACCCAGGAATTTTATGTAGAT  
TATAAACCCACCAACACGGAGACCAGCGAGATGCTGCTGAATGGGACGGGACCCTGCACCTAT  
AACAAATCGGGCTCCAGGGAGTGTGAGGTATGAACCATTGTGATAAAAAGAGCTCTTAAAGC  
TGGGAAATAAGTGGTGCTTTATTGAACTCTGGTGACTATCAAGGGAACGCGATGCCCCCCTC  
CCCTTCCCTCTCCCTCTCACTTTGGTGGAAGATCCTTCCTTGTCGGTTTTAGTGCATTTCATA  
ATACTGGTCATTTTCTCTCATACATAATCAACCCATTGAAATTTAAATACCACAATCAATGT  
GAAGCTTGAAGTCCGGTTTAATATAATACCTATTGTATAAGACCCTTTACTGATTCCATTAAT  
GTCGCATTTGTTTTAAGATAAAAGTCTTTTCATAGGTAAAAA

125/168

**FIGURE 125**

CCGTTATCGTCTTGCGCTACTGCTGAATGTCCGTCCCGGAGGAGGAGGAGGCTTTTGCCGC  
TGACCCAGAGATGGCCCCGAGCGAGCAAATTCCTACTGTCCGGCTGCGCGGCTACCGTGGCCG  
AGCTAGCAACCTTTCCCCTGGATCTCACAAAACCTCGACTCCAAATGCAAGGAGAAGCAGCTC  
TTGCTCGGTTGGGAGACGGTGCAAGAGAATCTGCCCCCTATAGGGGAATGGTGCGCACAGCCC  
TAGGGATCATTGAAGAGGAAGGCTTTCTAAAGCTTTGGCAAGGAGTGACACCCGCCATTTACA  
GACACGTAGTGTATTCTGGAGGTCGAATGGTCACATATGAACATCTCCGAGAGGTTGTGTTTG  
GCAAAAGTGAAGATGAGCATTATCCCCTTTGGAAATCAGTCATTGGAGGGATGATGGCTGGTG  
TTATTGGCCAGTTTTTAGCCAATCCAACTGACCTAGTGAAGGTTTCAGATGCAAATGGAAGGAA  
AAAGGAACTGGAAGGAAAACCATTGCGATTTTCGTGGTGTACATCATGCATTTGCAAAAATCT  
TAGCTGAAGGAGGAATACGAGGGCTTTGGGCAGGCTGGGTACCCAATATACAAAGAGCAGCAC  
TGGTGAATATGGGAGATTTAACCACCTTATGATACAGTGAAACACTACTTGGTATTGAATACAC  
CACTTGAGGACAATATCATGACTCACGGTTTATCAAGTTTATGTTCTGGACTGGTAGCTTCTA  
TTCTGGGAACACCAGCCGATGTCATCAAAGCAGAATAATGAATCAACCACGAGATAAACAAG  
GAAGGGGACTTTTGTATAAATCATCGACTGACTGCTTGATTTCAGGCTGTTCAAGGTGAAGGAT  
TCATGAGTCTATATAAAGGCTTTTTACCATCTTGGCTGAGAATGACCCCTTGGTCAATGGTGT  
TCTGGCTTACTTATGAAAAATCAGAGAGATGAGTGGAGTCAGTCCATTTTAA

127/168

**FIGURE 127**

CGCGGATCGGACCCAAGCAGGTCGGCGGGCGGCGGCAGGAGAGCGGCCGGGCGTCAGCTCCTCG  
ACCCCCGTGTCGGGCTAGTCCAGCGAGGCGGACGGGCGGCGTGGGCCCATGGCCAGGCCCGGC  
ATGGAGCGGTGGCGCGACCGGCTGGCGCTGGTGACGGGGGCGCTCGGGGGGCATCGGCGCGGCC  
GTGGCCCGGGCCCTGGTCCAGCAGGGACTGAAGGTGGTGGGCTGCGCCCGCACTGTGGGCAAC  
ATCGAGGAGCTGGCTGCTGAATGTAAGAGTGCAGGCTACCCCGGGACTTTGATCCCCTACAGA  
TGTGACCTATCAAATGAAGAGGACATCCTCTCCATGTTCTCAGCTATCCGTTCTCAGCACAGC  
GGTGTAGACATCTGCATCAACAATGCTGGCTTGGCCCGGCGCTGACACCCTGCTCTCAGGCAGC  
ACCAGTGGTTGGAAGGACATGTTCAATGTGAACGTGCTGGCCCTCAGCATCTGCACACGGGAA  
GCCTACCAGTCCATGAAGGAGCGGAATGTGGACGATGGGCACATCATTAACATCAATAGCATG  
TCTGGCCACCGAGTGTTACCCCTGTCTGTGACCCACTTCTATAGTGCCACCAAGTATGCCGTC  
ACTGCGCTGACAGAGGGACTGAGGCAAGAGCTTCGGGAGGCCAGACCCACATCCGAGCCACG  
TGCATCTCTCCAGGTGTGGTGGAGACACAATTCGCCTTCAAACCCGAGGATGTGGCCGAGGCTGTT  
AAGGCAGCTGCCACCTATGAGCAAATGAAGTGTCTCAAACCCGAGGATGTGGCCGAGGCTGTT  
ATCTACGTCCTCAGCACCCCGCACACATCCAGATTGGAGACATCCAGATGAGGCCACCGGAG  
CAGGTGACCTAGTGACTGTGGGAGCTCCTCCTTCCCTCCCCACCCTTCATGGCTTGCCTCCTG  
CCTCTGGATTTTAGGTGTTGATTTCTGGATCACGGGATACCACTTCCTGTCCACACCCCGACC  
AGGGGCTAGAAAATTTGTTTGAGATTTTATATCATCTTGTCAAATTGCTTCAGTTGTAAATG  
TGAAAAATGGGCTGGGGAAAGGAGGTGGTGTCCCTAATTGTTTTACTTGTTAACTTGTTCTTG  
TGCCCTGGGCACTTGGCCTTTGTCTGCTCTCAGTGTCTTCCCTTTGACATGGGAAAGGAGTT  
GTGGCCAAAATCCCCATCTTCTTGCACCTCAACGTCTGTGGCTCAGGGCTGGGGTGGCAGAGG  
GAGGCCTTCACCTTATATCTGTGTTGTTATCCAGGGCTCCAGACTTCCTCCTCTGCCTGCCCC  
ACTGCACCCTCTCCCCCTTATCTATCTCCTTCTCGGCTCCCCAGCCCAGTCTTGGCTTCTTGT  
CCCCTCCTGGGGTCATCCCTCCACTCTGACTCTGACTATGGCAGCAGAACACCAGGGCCTGGC  
CCAGTGGATTTTCATGGTGATCATTAAAAAGAAAAATCGCAACCAAAAAAAAAAAAA

129/168

**FIGURE 129**

AACTTCTACATGGGCCTCCTGCTGCTGGTGCTCTTCCTCAGCCTCCTGCCGGTGGCCTACACC  
ATCATGTCCCTCCCACCCTCCTTTGACTGCGGGCCGTTTCAGGTGCAGAGTCTCAGTTGCCCGG  
GAGCACCTCCCCTCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCCAGAATTCCAGTTCTGGTT  
TCATGCCAGCCTGTAAAAGGCCATGGAACCTTTGGGTGAATCACCGATGCCATTTAAGAGGGTT  
TTCTGCCAGGATGGAAATGTTAGGTCGTTCTGTGTCTGCGCTGTTCAATTCAGTAGCCACCAG  
CCACCTGTGGCCGTTGAGTGCTTGAAATGAGGAAGTGAAGAAATTAATTTCTCATGTATTTTT  
CTCATTTATTTATTAATTTTTTAAGTATAGTTGTACATATTTGGGGGTACATGTGATATTTGG  
ATACATGTATACAATATATAATGATCAAATCAGGGTAAGTGGGATATCCATCACATCAAACAT  
TTATTTTTTATTCTTTTTAGACAGAGTCTCACTCTGTCAACCAGGCTGGAGTGCAGTGGTGCC  
ATCTCAGCTTACTGCAACCTCTGCCTGCCAGGTTCAAGCGATTCTCATGCCTCCACCTCCCAA  
GTAGCTGGGACTACAGGCATGCACCACAATGCCCAACTAATTTTTGTATTTTTAGTAGAGACG  
GGGTTTTGCCATGTTGCCCAGGCTGGCCTTGAAGTCTGGCCTCAAACAATCCACTTGCCTCG  
GCCTCCCAAAGTGTTATGATTACAGGCGTGAGCCACCGTGCCTGGCCTAAACATTTATCTTTT  
CTTTGTGTTGGGAACCTTTGAAATTATACAATGAATTATTGTAACTGTCATCTCCCTGCTGTG  
CTATGGAACACTGGGACTTCTTCCCTCTATCTAACTGTATATTTGTACCAGTTAACCAACCGT  
ACTTCATCCCCACTCCTCTCTATCCTTCCCAACCTCTGATCACCTCATTCTACTCTCTACCTC  
CATGAGATCCACTTTTTTAGCTCCACATGTGAGTAAGAAAATGCAATATTTGTCTTTCTGTG  
CCTGGCTTATTTCACTTAACATAATGACTTCCTGTTCCATCCATGTTGCTGCAAATGACAGGA  
TTTCGTTCTTAATTTCAATTAAATAACCACACATGGCAAAAA

131/168

**FIGURE 131**

TTCTGAAGTAACGGAAGCTACCTTGTATAAAGACCTCAACACTGCTGACCATGATCAGCGCAG  
CCTGGAGCATCTTCCTCATCGGGACTAAAATTGGGCTGTTCCCTCAAGTAGCACCTCTATCAG  
TTATGGCTAAATCCTGTCCATCTGTGTGTCGGTGCGATGCGGGTTTCATTTACTGTAATGATC  
GCTTTCTGACATCCATTCCAACAGGAATACCAGAGGATGCTACAACCTCTCTACCTTCAGAACA  
ACCAAATAAATAATGCTGGGATTCCCTTCAGATTTGAAAACTTGCTGAAAGTAGAAAGAATAT  
ACCTATAACCACAACAGTTTAGATGAATTTCCCTACCAACCTCCCAAAGTATGTAAAAGAGTTAC  
ATTTGCAAGAAAATAACATAAGGACTATCACTTATGATTCACTTTCAAAAATTCCCTATCTGG  
AAGAATTACATTTAGATGACAACCTCTGTCTCTGCAGTTAGCATAGAAGAGGGAGCATTCCGAG  
ACAGCAACTATCTCCGACTGCTTTTCCTGTCCCGTAATCACCTTAGCACAATTCCCTGGGGTT  
TGCCAGGACTATAGAAGAACTACGCTTGGATGATAATCGCATATCCACTATTTTCATCACCAT  
CTCTTCAAGGTCTCACTAGTCTAAAACGCCTGGTTCTAGATGGAAACCTGTTGAACAATCATG  
GTTTAGGTGACAAAGTTTTCTTCAACCTAGTTAATTTGACAGAGCTGTCCCTGGTGCGGAATT  
CCCTGACTGCTGCACCAGTAAACCTTCCAGGCACAAACCTGAGGAAGCTTTATCTTCAAGATA  
ACCACATCAATCGGGTGCCCCCAATGCTTTTTCTTATCTAAGGCAGCTCTATCGACTGGATA  
TGTCCAATAATAACCTAAGTAATTTACCTCAGGGTATCTTTGATGATTTGGACAATATAACAC  
AACTGATTCTTCGCAACAATCCCTGGTATTGCGGGTGCAAGATGAAATGGGTACGTGACTGGT  
TACAATCACTACCTGTGAAGGTCAACGTGCGTGGGCTCATGTGCCAAGCCCCAGAAAAGGTTC  
GTGGGATGGCTATTAAGGATCTCAATGCAGAACTGTTTGATTGTAAGGACAGTGGGATTGTAA  
GCACCATTAGATAACCACTGCAATACCCAACACAGTGTATCCTGCCCAAGGACAGTGGCCAG  
CTCCAGTGACCAAACAGCCAGATATTAAGAACCCCAAGCTCACTAAGGATCAACAAACCACAG  
GGAGTCCCTCAAGAAAAACAATTACAATTACTGTGAAGTCTGTCACCTCTGATACCATTTCATA  
TCTCTTGAAACTTGCTCTACCTATGACTGCTTTGAGACTCAGCTGGCTTAACTGGGCCATA  
GCCCCGCATTTGGATCTATAACAGAAACAATTGTAACAGGGGAACGCAGTGAGTACTTGGTCA  
CAGCCCTGGAGCCTGATTCACCCTATAAAGTATGCATGGTTCCCATGGAAACCAGCAACCTCT  
ACCTATTTGATGAAACTCCTGTTTGTATTGAGACTGAAACTGCACCCCTTCGAATGTACAACC  
CTACAACCACCCTCAATCGAGAGCAAGAGAAAGAACCTTACAAAACCCCAATTTACCTTTGG  
CTGCCATCATTGGTGGGGCTGTGGCCCTGGTTACCATTGCCCTTCTTGCTTTAGTGTGTTGGT  
ATGTTCATAGGAATGGATCGCTCTTCTCAAGGAAGTGTGCATATAGCAAAGGGAGGAGAAGAA  
AGGATGACTATGCAGAAGCTGGCACTAAGAAGGACAACCTCTATCCTGGAAATCAGGGAACTT  
CTTTTCAGATGTTACCAATAAGCAATGAACCCATCTCGAAGGAGGAGTTTGTAATACACACCA  
TATTTCCCTCCTAATGGAATGAATCTGTACAAAACAATCACAGTGAAAGCAGTAGTAACCGAA  
GCTACAGAGACAGTGGTATTCCAGACTCAGATCACTCACACTCATGATGCTGAAGGACTCACA  
GCAGACTTGTGTTTTGGGTTTTTTTAAACCTAAGGGAGGTGATGGT

133/168

**FIGURE 133**

CCGTCATCCCCCTGCAGCCACCCTTCCCAGAGTCCTTTGCCAGGCCACCCCAGGCTTCTTGG  
CAGCCCTGCCGGGGCCACTTGTCTTCATGTCTGCCAGGGGGAGGTGGGAAGGAGGTGGGAGGAG  
GGCGTGCAGAGGCAGTCTGGGCTTGGCCAGAGCTCAGGGTGCTGAGCGTGTGACCAGCAGTGA  
GCAGAGGCCGGCCATGGCCAGCCTGGGGCTGCTGCTCCTGCTCTTACTGACAGCACTGCCACC  
GCTGTGGTCCTCCTCACTGCCTGGGCTGGACACTGCTGAAAGTAAAGCCACCATTGCAGACCT  
GATCCTGTCTGCGCTGGAGAGAGCCACCGTCTTCCTAGAACAGAGGCTGCCTGAAATCAACCT  
GGATGGCATGGTGGGGGTCCGAGTGCTGGAAGAGCAGCTAAAAAGTGTCCGGGAGAAGTGGGC  
CCAGGAGCCCCCTGCTGCAGCCGCTGAGCCTGCGCGTGGGGATGCTGGGGGAGAAGCTGGAGGC  
TGCCATCCAGAGATCCCTCCACTACCTCAAGCTGAGTGATCCCAAGTACCTAAGAGAGTTCCA  
GCTGACCCTCCAGCCCGGGTTTTTGGAAAGCTCCCACATGCCTGGATCCCACTGATGCCTCCTT  
GGTGTACCCACGTTCCGGGCCCCAGGACTCATTCTCAGAGGAGAGAAGTGACGTGTGCCTGGT  
GCAGCTGCTGGGAACCGGGACGGACAGCAGCGAGCCCTGCGGCCTCTCAGACCTCTGCAGGAG  
CCTCATGACCAAGCCCGGCTGCTCAGGCTACTGCCTGTCCCACCAACTGCTCTTCTTCCTCTG  
GGCCAGAATGAGGGGATGCACACAGGGACCACTCCAACAGAGCCAGGACTATATCAACCTCTT  
CTGCGCCAACATGATGGACTTGAACCGCAGAGCTGAGGCCATCGGATACGCCTACCCTACCCG  
GGACATCTTCATGGAAAACATCATGTTCTGTGGAATGGGCGGCTTCTCCGACTTCTACAAGCT  
CCGGTGGCTGGAGGCCATTCTCAGCTGGCAGAAACAGCAGGAAGGATGCTTCGGGGAGCCTGA  
TGCTGAAGATGAAGAATTATCTAAAGCTATTCAATATCAGCAGCATTTTTTCGAGGAGAGTGAA  
GAGGCGAGAAAAACAATTTCCAGATTCTCGCTCTGTTGCTCAGGCTGGAGTACAGTGGCGCAA  
TCTCGGCTCACTGCAACCTTTGCCTCCTGGGTTCAAGCAATTCTCTTGCCTCATCCTCCCGAG  
TAGCTGGGACTACAGGAGCGTGCCACCATACTGGCTAATTTTTATATTTTTTTTAGTAGAGAC  
AGGGTTTCATCATGTTGCTCATGCTGGTCTCGAACTCCTGATCTCAAGAGATCCGCCCACCTC  
AGGCTCCCAAAGTGTGGGATTATTAGGTGTGAGCCACCGTGTCTGGCTGAAAAGCACTTTCAA  
GAGACTGTGTTGAATAAAGGGCCAAGGTTCTTGCCACCCAGCACTCATGGGGGCTCTCTCCCC  
TAGATGGCTGCTCCTCCCACAACACAGCCACAGCAGTGGCAGCCCTGGGTGGCTTCCTATACA  
TCCTGGCAGAATACCCCCCAGCAAACAGAGAGCCACACCCATCCACACCGCCACCACCAAGCA  
GCCGCTGAGACGGACGGTTCATGCCAGCTGCCTGGAGGAGGAACAGACCCCTTTAGTCCTCA  
TCCCTTAGATCCTGGAGGGCACGGATCACATCCTGGGAAGAAGGCATCTGGAGGATAAGCAAA  
GCCACCCCGACACCCAATCTTGGAAGCCCTGAGTAGGCAGGGCCAGGGTAGGTGGGGGCCGGG  
AGGGACCCAGGTGTGAACGGATGAATAAAGTTCAACTGCAACTGAAAAA

135/168

**FIGURE 135**

GGTCTGAGTGCAGAGCTGCTGTCATGGCGGCCGCTCTGTGGGGCTTCTTTCCCGTCCTGCTGC  
TGCTGCTGCTATCGGGGGATGTCCAGAGCTCGGAGGTGCCCCGGGGCTGCTGCTGAGGGGATCGG  
GAGGGAGTGGGGTCGGCATAGGAGATCGCTTCAAGATTGAGGGGCGTGACAGTTGTTCCAGGGG  
TGAAGCCTCAGGACTGGATCTCGGCGGCCCGAGTGCTGGTAGACGGAGAAGAGCACGTCGGTT  
TCCTTAAGACAGATGGGAGTTTTGTGGTTCATGATATACCTTCTGGATCTTATGTAGTGGAAG  
TTGTATCTCCAGCTTACAGATTTGATCCCGTTCGAGTGGATATCACTTCGAAAGGAAAAATGA  
GAGCAAGATATGTGAATTACATCAAAACATCAGAGGTTGTCAGACTGCCCTATCCTCTCCAAA  
TGAAATCTTCAGGTCCACCTTCTTACTTTATTAAAGGGAATCGTGGGGCTGGACAGACTTTC  
TAATGAACCCAATGGTTATGATGATGGTTCTTCCTTTATTGATATTTGTGCTTCTGCCTAAAG  
TGGTCAACACAAGTGATCCTGACATGAGACGGGAAATGGAGCAGTCAATGAATATGCTGAATT  
CCAACCATGAGTTGCCTGATGTTTCTGAGTTCATGACAAGACTCTTCTCTTCAAAATCATCTG  
GCAAATCTAGCAGCGGCAGCAGTAAACAGGCAAAAGTGGGGCTGGCAAAGGAGGTAGTCAG  
GCCGTCCAGAGCTGGCATTTCACAAACACGGCAACACTGGGTGGCATCCAAGTCTTGGA  
CCGTGTGAAGCAACTACTATAAACTTGAGTCATCCCGACGTTGATCTCTTACAACTGTGTATGTT  
AACTTTTTAGCACATGTTTTGTACTTGGTACACGAGAAAACCCAGCTTTCATCTTTTGTCTGT  
ATGAGGTCAATATTGATGTCACTGAATTAATTACAGTGTCTTATAGAAAATGCCATTAATAAA  
TTATATGAACTACTATACATTATGTATATTAATTAACATCTTAATCCAGAAATCAAAAAA  
AAAAAAAAAAAAAAAAAAAAA

137/168

**FIGURE 137**

GATGGCGCAGCCACAGCTTCTGTGAGATTTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGAGGG  
GACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTCCCCAAA  
ACAAGTTTTGACATTTCCCCTGAAATGTCATTCTCTATCTATTCACTGCAAGTGCCTGCTGTT  
CCAGGCCTTACCTGCTGGGCACTAACGGCGGAGCCAGGATGGGGACAGAATAAAGGAGCCACG  
ACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATCTTCTCTTCACGGGAG  
GCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTCAGGCCTAAGATGAAAGCCTCTAGT  
CTTGCCTTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGGACTCCTTCCACTGGACTGAAG  
ACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTTCAGGAAATACGAAATGGATTTTCT  
GAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAACATTGACATCAGAATCTTAAGGAGGACT  
GAGTCTTTGCAAGACACAAAGCCTGCGAATCGATGCTGCCTCCTGCGCCATTTGCTAAGACTC  
TATCTGGACAGGGTATTTAAAACTACCAGACCCCTGACCATTATACTCTCCGGAAGATCAGC  
AGCCTCGCCAATTCCTTTCTTACCATCAAGAAGGACCTCCGGCTCTCTCATGCCCACATGACA  
TGCCATTGTGGGGAGGAAGCAATGAAGAAATACAGCCAGATTCTGAGTCACTTTGAAAAGCTG  
GAACCTCAGGCAGCAGTTGTGAAGGCTTTGGGGGAACTAGACATTCTTCTGCAATGGATGGAG  
GAGACAGAATAGGAGGAAAGTGATGCTGCTGCTAAGAATATTCGAGGTCAAGAGCTCCAGTCT  
TCAATACCTGCAGAGGAGGCATGACCCCAAACCACCATCTCTTTACTGTACTAGTCTTGTGCT  
GGTCACAGTGTATCTTATTTATGCATTACTTGCTTCCTTGCATGATTGTCTTTATGCATCCCC  
AATCTTAATTGAGACCATACTTGTATAAGATTTTTTGTAAATATCTTTCTGCTATTGGATATATT  
TATTAGTTAATATATTTATTTATTTTTTTGCTATTTAATGTATTTATTTTTTTACTTGACATG  
AACTTTAAAAAAATTACAGATTATATTTATAACCTGACTAGAGCAGGTGATGTATTTTTAT  
ACAGTAAAAAAAACCTTGTAATTTCTAGAAGAGTGGCTAGGGGGGTATTTCATTTGTAT  
TCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGATATTTGAAATTGAACCAATGAC  
TACTTAGGATGGGTGTGGAATAAGTTTTGATGTGGAATTGCACATCTACCTTACAATTACTG  
ACCATCCCCAGTAGACTCCCCAGTCCCATAATTGTGTATCTTCCAGCCAGGAATCCTACACGG  
CCAGCATGTATTTCTACAAATAAAGTTTTCTTGCATACCAAAAAAAAAAAAAAAAAAAAA



139/168

**FIGURE 139**

CCTGGAGCCGGAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGGTCCGGTTCCGCATCCAG  
CCTAGCGTGTCCACGATGCGGGCTGGGCTCCGGGACTTTTCGCTACCTGTTGCGTAGCGATCGAG  
GTGCTAGGGATCGCGGTCTTCCTTCGGGGATTCTTCCCGGCTCCCGTTTCGTTCTCTGCCAGA  
GCGGAACACGGAGCGGAGCCCCAGCGCCCGAACCCTCGGCTGGAGCCAGTTCTAACTGGACC  
ACGCTGCCACCACCTCTCTTCAGTAAAGTTGTTATTGTTCTGATAGATGCCTTGAGAGATGAT  
TTTGTGTTTGGGTCAAAGGGTGTGAAATTTATGCCCTACACAACCTTACCTTGTGGAAAAGGA  
GCATCTCACAGTTTTTGTGGCTGAAGCAAAGCCACCTACAGTTACTATGCCTCGAATCAAGGCA  
TTGATGACGGGGAGCCTTCCTGGCTTTGTGACGTCATCAGGAACCTCAATTCTCCTGCACTG  
CTGGAAGACAGTGTGATAAGACAAGCAAAAGCAGCTGGAAAAGAATAGTCTTTTATGGAGAT  
GAAACCTGGGTTAAATTATTCCCAAAGCATTTTGTGGAATATGATGGAACAACCTCATTTTTT  
GTGTCAGATTACACAGAGGTGGATAATAATGTCACGAGGCATTTGGATAAAGTATTAATAAAGA  
GGAGATTGGGACATATTAATCCTCCACTACCTGGGGCTGGACCACATTGGCCACATTTTCAGGG  
CCCAACAGCCCCCTGATTGGGCAGAAGCTGAGCGAGATGGACAGCGTGCTGATGAAGATCCAC  
ACCTCACTGCAGTCGAAGGAGAGAGAGACGCCTTTACCCAATTTGCTGGTTCTTTGTGGTGAC  
CATGGCATGTCTGAAACAGGAAGTCACGGGGCCTCCTCCACCGAGGAGGTGAATACACCTCTG  
ATTTTAATCAGTTCTGCGTTTGAAAGGAAACCCGGTGATATCCGACATCCAAAGCACGTCCAA  
**TAG**ACGGATGTGGCTGCGACACTGGCGATAGCACTTGGCTTACCGATTCCAAAAGACAGTGTA  
GGGAGCCTCCTATTCCCAGTTGTGGAAGGAAGACCAATGAGAGAGCAGTTGAGATTTTTTACAT  
TTGAATACAGTGCAGCTTAGTAACTGTTGCAAGAGAATGTGCCGTCATATGAAAAGATCCT  
GGGTTTGAGCAGTTTAAATGTGAGAAAGATTGCATGGGAACTGGATCAGACTGTACTTGGAG  
GAAAAGCATTACAGAAGTCCTATTCAACCTGGGCTCCAAGGTTCTCAGGCAGTACCTGGATGCT  
CTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCAGTTCTCACCCCTGCTCCTGCTCA  
GCGTCCCACAGGCACTGCACAGAAAGGCTGAGCTGGAAGTCCCACTGTCATCTCCTGGGTTTT  
CTCTGCTCTTTTATTTGGTGATCCTGGTTCTTTTCGGCCGTTTCACGTCATTGTGTGCACCTCAG  
CTGAAAGTTCGTGCTACTTCTGTGGCCTCTCGTGGCTGGCGGCAGGCTGCCTTTTCGTTTACCA  
GACTCTGGTTGAACACCTGGTGTGTGCCAAGTGCTGGCAGTGCCCTGGACAGGGGGCCTCAGG  
GAAGGACGTGGAGCAGCCTTATCCCAGGCCTCTGGGTGTCCCGACACAGGTGTTTACATCTGT  
GCTGTCAGGTCAGATGCCTCAGTTCTTGGAAGCTAGGTTCTGCGACTGTTACCAAGGTGAT  
TGTAAGAGCTGGCGGTCACAGAGGAACAAGCCCCCAGCTGAGGGGGTGTGTGAATCGGACA  
GCCTCCCAGCAGAGGTGTGGGAGCTGCAGCTGAGGGAAGAAGAGACAATCGGCCTGGACACTC  
AGGAGGGTCAAAGGAGACTTGGTCGCACCACTCATCCTGCCACCCCCAGAATGCATCCTGCC  
TCATCAGGTCCAGATTTCTTTCCAAGGCGACGTTTTCTGTTGGAATTCTTAGTCTTTGGCCT  
CGGACACCTTCATTGCTTAGCTGGGGAGTGGTGGTGAGGCAGTGAAGAAGAGGCGGATGGTCA  
CACTCAGATCCACAGAGCCCAGGATCAAGGGACCACTGCAGTGGCAGCAGGACTGTTGGGCC  
CCCACCCCAACCCTGCACAGCCCTCATCCCCTCTTGCTTGAGCCGTCAGAGGCCCTGTGCTG  
AGTGTCTGACCGAGACACTCACAGCTTTGTCATCAGGGCACAGGCTTCCTCGGAGCCAGGATG  
ATCTGTGCCACGCTTGACCTCGGGCCCATCTGGGCTCATGCTCTCTCTCCTGCTATTGAATT  
AGTACCTAGCTGCACACAGTATGTAGTTACCAAAGAATAAACGGCAATAATTGAGAAAAAAA

141/168

**FIGURE 141**

GGCACGAGGCAAGCCTTCCAGGTTATCGTGACGCACCTTGAAAGTCTGAGAGCTACTGCCCTA  
CAGAAAGTTACTAGTGCCCTAAAGCTGGCGCTGGCACTGATGTACTGCTGCTGTTGGAGTAC  
AACTTCCCTATAGAAAACAAGTCCAGCACCTTAAGACCACTCACACCTTCAGAGTGAAGAAC  
TTAAACCCGAAGAAATTCAGCATTTCATGACCAGGATCACAAAGTACTGGTCCTGGACTCTGGG  
AATCTCATAGCAGTTCCAGATAAAAACTACATACGCCCAGAGATCTTCTTTGCATTAGCCTCA  
TCCTTGAGCTCAGCCTCTGCGGAGAAAGGAAGTCCGATTCTCCTGGGGGTCTCTAAAGGGGAG  
TTTTGTCTCTACTGTGACAAGGATAAAGGACAAAGTCATCCATCCCTTCAGCTGAAGAAGGAG  
AAACTGATGAAGCTGGCTGCCCAAAGGAATCAGCACGCCGGCCCTTCATCTTTTATAGGGCT  
CAGGTGGGCTCCTGGAACATGCTGGAGTCGGCGGCTCACCCCGGATGGTTCATCTGCACCTCC  
TGCAATTGTAATGAGCCTGTTGGGGTGACAGATAAATTTGAGAACAGGAAACACATTGAATTT  
TCATTTCAACCAGTTTGCAAAGCTGAAATGAGCCCCAGTGAGGTCAGCGATTAGGAAACTGCC  
CCATTGAACGCCTTCCTCGCTAATTTGAACTAATTGTATAAAAACACCAAACCTGCTCACT

**FIGURE 143**

[illegible]

145/168

**FIGURE 145**

CTGTGCAGCTCGAGGCTCCAGAGGCACACTCCAGAGAGAGCCAAGGTTCTGACGCGATGAGGA  
AGCACCTGAGCTGGTGGTGGCTGGCCACTGTCTGCATGCTGCTCTTCAGCCACCTCTCTGCGG  
TCCAGACGAGGGGCATCAAGCACAGAATCAAGTGGAACCGGAAGGCCCTGCCCAGCACTGCCC  
AGATCACTGAGGCCAGGTGGCTGAGAACCGCCCCGGGAGCCTTCATCAAGCAAGGCCGCAAGC  
TCGACATTGACTTCGGAGCCGAGGGCAACAGGTACTACGAGGCCAACTACTGGCAGTTCCCCG  
ATGGCATCCACTACAACGGCTGCTCTGAGGCTAATGTGACCAAGGAGGCATTTGTCACCGGCT  
GCATCAATGCCACCCAGGCGGCGAACCAGGGGGAGTTCCAGAAGCCAGACAACAAGCTCCACC  
AGCAGGTGCTCTGGCGGCTGGTCCAGGAGCTCTGCTCCCTCAAGCATTGCGAGTTTTGGTTGG  
AGAGGGGCGCAGGACTTCGGGTCACCATGCACCAGCCAGTGCTCCTCTGCCTTCTGGCTTTGA  
TCTGGCTCATGGTGAAATTAAGCTTGCCAGGAGGCTGGCAGTACAGAGCGCAGCAGCGAGCAAA  
TCCTGGCAAGTGACCCAGCTCTTCTCCCCCAAACCCACGCGTGTCTGAAGGTGCCCAGGAGC  
GGCGATGCACTCGCACTGCAAATGCCGCTCCCACGTATGCGCCCTGGTATGTGCCTGCGTTCT  
GATAGATGGGGGACTGTGGCTTCTCCGTCACTCCATTCTCAGCCCCTAGCAGAGCGTCTGGCA  
CACTAGATTAGTAGTAAATGCTTGATGAGAAGAACACATCAGGCACTGCGCCACCTGCTTCAC  
AGTACTTCCCAACAACTCTTAGAGGTAGGTGTATTCCCGTTTTACAGATAAGGAAACTGAGGC  
CCAGAGAGCTGAAGTACTGCACCCAGCATCACCAGCTAGAAAGTGGCAGAGCCAGGATTCAAC  
CCTGGCTTGTCTAACCCAGGTTTTCTGCTCTGTCCAATTCCAGAGCTGTCTGGTGATCACTT  
TATGTCTCACAGGGACCCACATCCAAACATGTATCTCTAATGAAATTGTGAAAGCTCCATGTT  
TAGAAATAAATGAAAACACCTGA

147/168

**FIGURE 147**

GCCTTGGCCTCCCAAAGGGCTGGGATTATAGGCGTGACCACCATGTCTGGTCCAGAGTCTCAT  
TTCCTGATGATTTATAGACTCAAAGAAAAC**TATG**TTTCAGAAGCTCTCTTCTCTTCTGGCCTC  
CTCTCTGTCTTCTTTCCCTCTTTCTTCTTATTTTAATTAGTAGCATCTACTCAGAGTCATGCA  
AGCTGGAAATCTTTCATTTTGCTTGTCAGTGGGGTAGGTCACTGAGTCTTAGTTTTTATTTTT  
TGAAATTTCAACTTTCAGATTCAGGGGGTACATGTGAAGGTTTGTTTTATGAGTATATTGCAT  
**GATGCTGAGGTTTGGGGT**

149/168

**FIGURE 149**

GTCTCCGCGTCACAGGAAGCTTCAGCACCCACAGGGCGGACAGCGCTCCCCTCTACCTGGAGAC  
TTGACTCCCGCGCGCCCCAACCCCTGCTTATCCCTTGACCGTCGAGTGTCAGAGATCCTGCAGC  
CGCCCAGTCCCGGCCCTCTCCCGCCCCACACCCACCCTCCTGGCTCTTCCTGTTTTTACTCC  
TCCTTTTTCATTACATAACAAAAGCTACAGCTCCAGGAGCCCAGCGCCGGGCTGTGACCCAAGCC  
GAGCGTGGAAGAATGGGGTTCCCTCGGGACCGGCACTTGGATTCTGGTGTTAGTGCTCCCGATT  
CAAGCTTTCCCCAACCTGGAGGAAGCCAAGACAAATCTCTACATAATAGAGAATTAAGTGCA  
GAAAGACCTTTGAATGAACAGATTGCTGAAGCAGAAGAAGACAAGATTAAAAAACATATCCT  
CCAGAAAACAAGCCAGGTCAGAGCAACTATTCTTTTGTGATACTTGAACCTGCTAAAGGCA  
ATAACAGAAAAGGAAAAAATTGAGAAAGAAAGACAATCTATAAGAAGCTCCCCACTTGATAAT  
AAGTTGAATGTGGAAGATGTTGATTCAACCAAGAATCGAAAAGTATCGATGATTATGACTCT  
ACTAAGAGTGGATTGGATCATAAATTTCAAGATGATCCAGATGGTCTTCATCAACTAGACGGG  
ACTCCTTTAACCGCTGAAGACATTGTCCATAAAATCGCTGCCAGGATTTATGAAGAAAATGAC  
AGAGCCGTGTTTGACAAGATTGTTTCTAACTACTTAATCTCGGCCTTATCACAGAAAGCCAA  
GCACATACACTGGAAGATGAAGTAGCAGAGGTTTTACAAAAATTAATCTCAAAGGAAGCCAAC  
AATTATGAGGAGGATCCCAATAAGCCCACAAGCTGGACTGAGAATCAGGCTGGAAAAATACCA  
GAGAAAGTGACTCCAATGGCAGCAATTCAAGATGGTCTTGCTAAGGGAGAAAACGATGAAACA  
GTATCTAACACATTAACCTTGACAAATGGCTTGGAAGGAGAACTAAAACCTACAGTGAAGAC  
AACTTTGAGGAACTCCAATATTTCCCAAATTTCTATGCGCTACTGAAAAGTATTGATTCAGAA  
AAAGAAGCAAAAGAGAAAGAAACACTGATTACTATCATGAAAACACTGATTGACTTTGTGAAG  
ATGATGGTGAAATATGGAACAATATCTCCAGAAGAAGGTGTTTCCTACCTTGAAAAGCTTGGAT  
GAAATGATTGCTCTTCAGACCAAAAACAAGCTAGAAAAAATGCTACTGACAATATAAGCAAG  
CTTTTCCCAGCACCATCAGAGAAGAGTCATGAAGAAACAGACAGTACCAAGGAAGAAGCAGCT  
AAGATGGAAAAGGAATATGGAAGCTTGAAGGATTCCACAAAAGATGATACTCCAACCCAGGA  
GGAAAGACAGATGAACCCAAAGGAAAAACAGAAGCCTATTTGGAAGCCATCAGAAAAAATATT  
GAATGGTTGAAGAAACATGACAAAAAGGGAAATAAAGAAGATTATGACCTTTCAAAGATGAGA  
GACTTCATCAATAACAAGCTGATGCTTATGTGGAGAAAGGCATCCTTGACAAGGAAGAAGCC  
GAGGCCATCAAGCGCATTTATAGCAGCCTGTAAAAATGGCAAAGATCCAGGAGTCTTTCAAC  
TGTTTCAGAAAACATAATATAGCTTAAAACACTTCTAATTCTGTGATTAAATTTTTTGACCC  
AAGGGTTATTAGAAAGTGCTGAATTTACAGTAGTTAACCTTTTACAAGTGGTTAAACATAGC  
TTTCTTCCCGTAAAACTATCTGAAAGTAAAGTTGTATGTAAGCTGAAAAAAAAAAAAAAAAAA  
AAA

151/168

**FIGURE 151**

CGGCTCGAGGCTCCCGCCAGGAGAAAGGAACATTCTGAGGGGAGTCTACACCCTGTGGAGCTC  
AAGATGGTCTGAGTGGGGCGCTGTGCTTCCGAATGAAGGACTCGGCATTGAAGGTGCTTTAT  
CTGCATAATAACCAGCTTCTAGCTGGAGGGCTGCATGCAGGGAAGGTCATTAAAGGTGAAGAG  
ATCAGCGTGGTCCCCAATCGGTGGCTGGATGCCAGCCTGTCCCCCGTCATCCTGGGTGTCCAG  
GGTGGAAGCCAGTGCCTGTCATGTGGGGTGGGGCAGGAGCCGACTCTAACACTAGAGCCAGTG  
AACATCATGGAGCTCTATCTTGGTGCCAAGGAATCCAAGAGCTTCACCTTCTACCGGCGGGAC  
ATGGGGCTCACCTCCAGCTTCGAGTGGCTGCCTACCGGGGCTGGTTCCTGTGCACGGTGCCT  
GAAGCCGATCAGCCTGTCAGACTCACCCAGCTTCCCGAGAATGGTGGCTGGAATGCCCCATC  
ACAGACTTCTACTTCCAGCAGTGTGACTAGGGCAACGTGCCCCCAGAAGTCCCTGGGCAGAG  
CCAGCTCGGGTGAGGGGTGAGTGGAGGAGACCCATGGCGGACAATCACTCTCTCTGCTCTCAG  
GACCCCCACGTCTGACTTAGTGGGCACCTGACCACTTTGTCTTCTGGTTCCCAGTTTGGATAA  
ATTCTGAGATTTGGAGCTCAGTCCACGGTCTCCCCCACTGGATGGTGCTACTGCTGTGGAAC  
CTTGTA AAAACCATGTGGGGTAAACTGGGAATAACATGAAAAGATTTCTGTGGGGGTGGGGTG  
GGGAGTGGTGGGAATCATTCCTGCTTAATGGTAAGTGTACCTGAGCCCCGCAG  
GCCAACCCATCCCCAGTTGAGCCTTATAGGGTCAGTAGCTCTCCACATGAAGTCTGTCACTC  
ACCACTGTGCAGGAGAGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCTTGGCCCAGCCCC  
ACCCCTTCCCTTTAATCCTGCCACTGTCATATGCTACCTTTCCTATCTCTTCCCTCATCATC  
TTGTTGTGGGCATGAGGAGGTGGTGATGTCAGAAGAAATGGCTCGAGCTCAGAAGATAAAAGA  
TAAGTAGGGTATGCTGATCCTCTTTTAAAAACCCAAGATACAATCAAAATCCCAGATGCTGGT  
CTCTATTCCCATGAAAAAGTGCTCATGACATATTGAGAAGACCTACTTACAAAGTGGCATATA  
TTGCAATTTATTTTAATTA AAAAGATACCTATTTATATATTTCTTTATAGAAAAAGTCTGGAA  
GAGTTTACTTCAATTGTAGCAATGTCAGGGTGGTGGCAGTATAGGTGATTTTTCTTTTAATTC  
TGTTAATTTATCTGTATTTCTTAATTTTCTACAATGAAGATGAATTCCTTGTATAAAAAATAA  
GAAAAGAAATTAATCTTGAGGTAAGCAGAGCAGACATCATCTCTGATTGTCCTCAGCCTCCAC  
TTCCCCAGAGTAAATTCAAATTGAATCGAGCTCTGCTGCTCTGGTTGGTTGTAGTAGTGATCA  
GGAAACAGATCTCAGCAAAGCCACTGAGGAGGAGGCTGTGCTGAGTTTGTGTGGCTGGAATCT  
CTGGGTAAGGAACCTTAAAGAACAAAATCATCTGGTAATTCTTTCCTAGAAGGATCACAGCCC  
CTGGGATTCCAAGGCATTGGATCCAGTCTCTAAGAAGGCTGCTGTACTGGTTGAATTGTGTCC  
CCCTCAAATTCACATCCTTCTTGGAATCTCAGTCTGTGAGTTTATTTGGAGATAAGGTCTCTG  
CAGATGTAGTTAGTTAAGACAAGGTCATGCTGGATGAAGGTAGACCTAAATTCAATATGACTG  
GTTTCCTTGTATGAAAAGGAGAGGACACAGAGACAGAGGAGACGCGGGGAAGACTATGTAAAG  
ATGAAGGCAGAGATCGGAGTTTTGCAGCCACAAGCTAAGAAACACCAAGGATTGTGGCAACCA  
TCAGAAGCTTGGAAGAGGCAAAGAAGAATTCTTCCCTAGAGGCTTTAGAGGGATAACGGCTCT  
GCTGAAACCTTAATCTCAGACTTCCAGCCTCCTGAACGAAGAAAGAATAAATTTTCGGCTGTTT  
TAAGCCACCAAGGATAAATTGGTTACAGCAGCTCTAGGAACTAATACAGCTGCTAAAATGATC  
CCTGTCTCCTCGTGTTTACATTCTGTGTGTGTCCCCTCCCACAATGTACCAAAGTTGTCTTTG  
TGACCAATAGAATATGGCAGAAGTGATGGCATGCCACTTCCAAGATTAGGTTATAAAAGACAC  
TGCAGCTTCTACTTGAGCCCTCTCTCTGCCACCCACCGCCCCAATCTATCTTGGCTCACT  
CGCTCTGGGGGAAGCTAGCTGCCATGCTATGAGCAGGCCTATAAAGAGACTTACGTGGTAAAA  
AATGAAGTCTCCTGCCCACAGCCACATTAGTGAACCTAGAAGCAGAGACTCTGTGAGATAATC  
GATGTTTGTGTTTAAAGTTGCTCAGTTTTGGTCTAACTTGTTATGCAGCAATAGATAAATAA  
TATGCAGAGAAAGAG

153/168

**FIGURE 153**

CTTCAGAACAGGTTCTCCTTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCTGCAATGGCC  
GCCCTGCAGAAATCTGTGAGCTCTTTCCTTATGGGGACCCTGGCCACCAGCTGCCTCCTTCTC  
TTGGCCCTCTTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCCAGTGCAGGCTTGACAAG  
TCCAACCTCCAGCAGCCCTATATCACCAACCGCACCTTCATGCTGGCTAAGGAGGCTAGCTTG  
GCTGATAACAACACAGACGTTTCGTCTCATTGGGGAGAACTGTTCCACGGAGTCAGTATGAGT  
GAGCGCTGCTATCTGATGAAGCAGGTGCTGAACTTCACCCTTGAAGAAGTGCTGTTCCCTCAA  
TCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGCCCTTCCTGGCCAGGCTCAGCAACAGG  
CTAAGCACATGTCATATTGAAGGTGATGACCTGCATATCCAGAGGAATGTGCAAAAGCTGAAG  
GACACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATCAAAGCAATTGGAGAACTGGATTTGCTG  
TTTATGTCTCTGAGAAATGCCTGCATTTGACCAGAGCAAAGCTGAAAAATGAATAACTAACCC  
CCTTTCCCTGCTAGAAATAACAATTAGATGCCCCAAAGCGATTTTTTTTAAACCAAAGGAAGA  
TGGGAAGCCAACTCCATCATGATGGGTGGATTCCAAATGAACCCCTGCGTTAGTTACAAAGG  
AAACCAATGCCACTTTTGTTTATAAGACCAGAAGGTAGACTTTCTAAGCATAGATATTTATTG  
ATAACATTTTCATTGTAAGTGGTGTCTATACACAGAAAACAATTTATTTTTTAAATAATTGTC  
TTTTTCCATAAAAAAGATTACTTTCCATTCCTTTAGGGGAAAAAACCCCTAAATAGCTTCATG  
TTCCATAATCAGTACTTTATATTTATAAATGTATTTATTATTATAAGACTGCATTTTAT  
TTATATCATTTTATTAATATGGATTTATTTATAGAAACATCATTCGATATTGCTACTTGAGTG  
TAAGGCTAATATTGATATTTATGACAATAATTATAGAGCTATAACATGTTTATTTGACCTCAA  
TAAACACTTGGATATCCC



155/168

**FIGURE 155**

GGCTTGCTGAAAATAAAATCAGGACTCCTAACCTGCTCCAGTCAGCCTGCTTCCACGAGGCCT  
GTCAGTCAGTGCCCGACTTGTGACTGAGTGTGCAGTGCCAGCATGTACCAGGTCAGTGCAGA  
GGGCTGCCTGAGGGCTGTGCTGAGAGGGAGAGGAGCAGAGATGCTGCTGAGGGTGGAGGGAGG  
CCAAGCTGCCAGGTTTGGGGCTGGGGGCCAAGTGGAGTGAGAACTGGGATCCCAGGGGGAGG  
GTGCAGATGAGGGAGCGACCCAGATTAGGTGAGGACAGTTCTCTCATTAGCCTTTTCCTACAG  
GTGGTTGCATTCTTGCAATGGTCATGGGAACCCACACCTACAGCCA'CTGGCCCAGCTGCTGC  
CCCAGCAAAGGGCAGGACACCTCTGAGGAGCTGCTGAGGTGGAGCACTGTGCCTGTGCCTCCC  
CTAGAGCCTGCTAGGCCCAACCGCCACCCAGAGTCCTGTAGGGCCAGTGAAGATGGACCCCTC  
AACAGCAGGGCCATCTCCCCCTGGAGATATGAGTTGGACAGAGACTTGAACCGGCTCCCCAG  
GACCTGTACCACGCCCGTTGCCTGTGCCCGCACTGCGTCAGCCTACAGACAGGCTCCACATG  
GACCCCCGGGGCAACTCGGAGCTGCTCTACCACAACCAGACTGTCTTCTACAGGCGGCCATGC  
CATGGCGAGAAGGGCACCCACAAGGGCTACTGCCTGGAGCGCAGGCTGTACCGTGTTTCCTTA  
GCTTGTGTGTGTGTGCGGCCCCGTGTGATGGGCTAGCCGGACCTGCTGGAGGCTGGTCCCTTT  
TTGGGAAACCTGGAGCCAGGTGTACAACCACTTGCCATGAAGGGCCAGGATGCCCAGATGCTT  
GGCCCCGTGTGAAGTGCTGTCTGGAGCAGCAGGATCCCGGGACAGGATGGGGGGCTTTGGGGAA  
AACCTGCACTTCTGCACATTTTGAAAAGAGCAGCTGCTGCTTAGGGCCGCCGAAGCTGGTGT  
CCTGTCATTTTCTCTCAGGAAAGGTTTTCAAAGTTCTGCCATTTCTGGAGGCCACCACTCCT  
GTCTCTTCCTCTTTTCCCATCCCCTGCTACCCTGGCCCAGCACAGGCACTTTCTAGATATTTT  
CCCCTTGCTGGAGAAGAAAGAGCCCCTGGTTTTATTTGTTTGTTTACTCATCACTCAGTGAGC  
ATCTACTTTGGGTGCATTCTAGTGTAGTTACTAGTCTTTTGACATGGATGATTCTGAGGAGGA  
AGCTGTTATTGAATGTATAGAGATTTATCCAAATAAATATCTTTATTTAAAAATGAAAAA

157/168

**FIGURE 157**

CCGGCGATGTCGCTCGTGCTGCTAAGCCTGGCCGCGCTGTGCAGGAGCGCCGTACCCCGAGAG  
CCGACCGTTCAATGTGGCTCTGAAACTGGGCCATCTCCAGAGTGGATGCTACAACATGATCTA  
ATCCCGGAGACTTGAGGGACCTCCGAGTAGAACCTGTTACAACAGTGTGCAACAGGGGAC  
TATTCAATTTTGATGAATGTAAGCTGGGTACTCCGGGCAGATGCCAGCATCCGCTTGTTGAAG  
GCCACCAAGATTTGTGTGACGGGCAAAGCAACTTCCAGTCCTACAGCTGTGTGAGGTGCAAT  
TACACAGAGGCCTTCCAGACTCAGACCAGACCCTCTGGTGGTAAATGGACATTTTCCTACATC  
GGCTTCCCTGTAGAGCTGAACACAGTCTATTTTCATTGGGGCCCATATATTCCTAATGCAAAT  
ATGAATGAAGATGGCCCTTCCATGTCTGTGAATTTACCTCACCAAGGCTGCCTAGACCACATA  
ATGAAATATAAAAAAAGTGTGTCAAGGCCGGAAGCCTGTGGGATCCGAACATCACTGCTTGT  
AAGAAGAATGAGGAGACAGTAGAAGTGAACCTCACAACTCCCTGGGAAACAGATACATG  
GCTCTTATCCAACACAGCACTATCATCGGGTTTTCTCAGGTGTTTGAGCCACACCAGAAGAAA  
CAAACGCGAGCTTCAGTGGTGATTCCAGTGACTGGGGATAGTGAAGGTGCTACGGTGCAGCTG  
ACTCCATATTTTCCTACTTGTGGCAGCGACTGCATCCGACATAAAGGAACAGTTGTGCTCTGC  
CCACAAACAGGCGTCCCTTTCCCTCTGGATAACAACAAAAGCAAGCCGGGAGGCTGGCTGCCT  
CTCCTCCTGCTGTCTCTGCTGGTGGCCACATGGGTGCTGGTGGCAGGGATCTATCTAATGTGG  
AGGCACGAAAGGATCAAGAAGACTTCCTTTTCTACCACCACACTACTGCCCCCATTAAGGTT  
CTTGTGGTTTACCCATCTGAAATATGTTTCCATCACACAATTTGTTACTTCACTGAATTTCTT  
CAAAACCATTCGAGAAGTGAGGTCATCCTTGAAAAGTGGCAGAAAAAGAAAATAGCAGAGATG  
GGTCCAGTGCAGTGGCTTGCCACTCAAAGAAGGCAGCAGACAAAGTCGTCTTCCTTCTTTCC  
AATGACGTCAACAGTGTGTGCGATGGTACCTGTGGCAAGAGCGAGGGCAGTCCCAGTGAGAAC  
TCTCAAGACCTCTTCCCCCTTGCCTTTAACCTTTTCTGCAGTGATCTAAGAAGCCAGATTCAT  
CTGCACAAATACGTGGTGGTCTACTTTAGAGAGATTGATACAAAGACGATTACAATGCTCTC  
AGTGTCTGCCCCAAGTACCACCTCATGAAGGATGCCACTGCTTTCTGTGCAGAACTTCTCCAT  
GTCAAGCAGCAGGTGTCAGCAGGAAAAAGATCACAAAGCCTGCCACGATGGCTGCTGCTCCTTG  
**TAG**

159/168

**FIGURE 159**

AGCCACCAGCGCAACATGACAGTGAAGACCCTGCATGGCCCAGCCATGGTCAAGTACTTGCTG  
CTGTCGATATTGGGGCTTGCCTTTCTGAGTGAGGCGGCAGCTCGGAAAATCCCCAAAGTAGGA  
CATACTTTTTTCCAAAAGCCTGAGAGTTGCCCGCCTGTGCCAGGAGGTAGTATGAAGCTTGAC  
ATTGGCATCATCAATGAAAACCAGCGCGTTTCCATGTCACGTAACATCGAGAGCCGCTCCACC  
TCCCCCTGGAATTACACTGTCACTTGGGACCCCAACCGGTACCCCTCGGAAGTTGTACAGGCC  
CAGTGTAGGAACCTGGGCTGCATCAATGCTCAAGGAAAGGAAGACATCTCCATGAATTCCGTT  
CCCATCCAGCAAGAGACCCTGGTCGTCCGGAGGAAGCACCAAGGCTGCTCTGTTTCTTTCCAG  
TTGGAGAAGGTGCTGGTGACTGTTGGCTGCACCTGCGTCACCCCTGTCATCCACCATGTGCAG  
TAAGAGGTGCATATCCACTCAGCTGAAGAAG

161/168

**FIGURE 161**

ACACTGGCCAAACAAAAACGAAAGCACTCCGTGCTGGAAGTAGGAGGAGAGTCAGGACTCCCA  
GGACAGAGAGTGCACAACTACCCAGCACAGCCCCCTCCGCCCCCTCTGGAGGCTGAAGAGGG  
ATTCCAGCCCCCTGCCACCCACAGACACGGGGCTGACTGGGGTGTCTGCCCCCCTTGGGGGGGGG  
CAGCACAGGGCCTCAGGCCTGGGTGCCACCTGGCACCTAGAAGATGCTGTGCCCTGGTTCTT  
GCTGTCCTTGGCACTGGGCGCAAGCCCACTGGTCTTTCTCTGGAGAGGCTTGTGGGGCCTCA  
GGACGCTACCCACTGCTCTCCGGGCCTCTCCTGCCGCCTCTGGGACAGTGACATACTCTGCCT  
GCCTGGGGACATCGTGCCTGCTCCGGGCCCCGTGCTGGCGCCTACGCACCTGCAGACAGAGCT  
GGTGCTGAGGTGCCAGAAGGAGACCGACTGTGACCTCTGTCTGCGTGTGGCTGTCCACTTGGC  
CGTGCAATGGGCACTGGGAAGAGCCTGAAGATGAGGAAAAGTTTGGAGGAGCAGCTGACTCAGG  
GGTGGAGGAGCCTAGGAATGCCTCTCTCCAGGCCCAAGTCGTGCTCTCCTTCCAGGCCTACCC  
TACTGCCCGCTGCGTCTCTGCTGGAGGTGCAAGTGCCTGCTGCCCTTGTGCAGTTTGGTCACTC  
TGTGGGCTCTGTGGTATATGACTGCTTCGAGGCTGCCCTAGGGAGTGAGGTACGAATCTGGTC  
CTATACTCAGCCCAGGTACGAGAAGGAACTCAACCACACACAGCAGCTGCCTGCCCTGCCCTG  
GCTCAACGTGTCAGCAGATGGTGACAACGTGCATCTGGTTCTGAATGTCTCTGAGGAGCAGCA  
CTTCGGCCTCTCCCTGTACTGGAATCAGGTCCAGGGCCCCCCTAAAACCCCGGTGGCACAAAA  
CCTGACTGGACCGCAGATCATTACCTTGAACCACACAGACCTGGTTCCCTGCCTCTGTATTCA  
GGTGTGGCCTCTGGAACCTGACTCCGTTAGGACGAACATCTGCCCTTCAGGGAGGACCCCCG  
CGCACACCAGAACCTCTGGCAAGCCGCCCCGACTGCGACTGCTGACCCTGCAGAGCTGGCTGCT  
GGACGCACCGTGCTCGCTGCCCGCAGAAGCGGCACTGTGCTGGCGGGCTCCGGGTGGGGACCC  
CTGCCAGCCACTGGTCCCACCGCTTTCTGGGAGAACGTCACTGTGGACAAGGTTCTCGAGTT  
CCCATTGCTGAAAGGCCACCCTAACCTCTGTGTTTCAAGTGAACAGCTCGGAGAAGCTGCAGCT  
GCAGGAGTGCTTGTGGGCTGACTCCCTGGGGCCTCTCAAAGACGATGTGCTACTGTTGGAGAC  
ACGAGGGCCCCCAGGACAACAGATCCCTCTGTGCCTTGAACCCAGTGGCTGTACTTCACTACC  
CAGCAAAGCCTCCACGAGGGCAGCTCGCCTTGGAGAGTACTTACTACAAGACCTGCAGTCAGG  
CCAGTGTCTGCAGCTATGGGACGATGACTTGGGAGCGCTATGGGCCTGCCCCATGGACAAATA  
CATCCACAAGCGCTGGGCCCTCGTGTGGCTGGCCTGCCTACTCTTTGCCGCTGCGCTTTCCCT  
CATCCTCCTTCTCAAAAAGGATCACGCGAAAGGGTGGCTGAGGCTCTTGAAACAGGACGTCCG  
CTCGGGGGCGGCCGCCAGGGGGCGCGCGGCTCTGCTCCTCTACTCAGCCGATGACTCGGGTTT  
CGAGCGCCTGGTGGGCGCCCTGGCGTCGGCCCTGTGCCAGCTGCCGCTGCGCGTGGCCGTAGA  
CCTGTGGAGCCGTCTGAACTGAGCGCGCAGGGGCCCGTGGCTTGGTTTACGCGCAGCGGCG  
CCAGACCCTGCAGGAGGGCGGCGTGGTGGTCTTGCTCTTCTCTCCCGGTGCGGTGGCGCTGTG  
CAGCGAGTGGCTACAGGATGGGGTGTCCGGGCCCCGGGCGCACGGCCCCGCACGACGCCTTCCG  
CGCCTCGCTCAGCTGCGTGCTGCCCCGACTTCTTGAGGGCCGGGCGCCCCGGCAGCTACGTGGG  
GGCCTGCTTCGACAGGCTGCTCCACCCGGACGCCGTACCCGCCCTTTTCCGCACCGTGCCCGT  
CTTCACACTGCCCTCCCAACTGCCAGACTTCTGGGGGCCCTGCAGCAGCCTCGCGCCCCGCG  
TTCCGGGGCGGCTCCAAGAGAGAGCGGAGCAAGTGTCCCGGGCCCTTCAGCCAGCCCTGGATAG  
CTACTTCCATCCCCCGGGGACTCCCGCGCCGGGACGCGGGGTGGGACCAGGGGCGGGACCTGG  
GGCGGGGGACGGGACTTAAATAAAGGCAGACGCTGTTTTTCTAAAAAAA

163/168

**FIGURE 163**

GGGAGGGCTCTGTGCCAGCCCCGATGAGGACGCTGCTGACCATCTTGACTGTGGGATCCCTGG  
CTGCTCACGCCCCCTGAGGACCCCTCGGATCTGCTCCAGCACGTGAAATTCCAGTCCAGCAACT  
TTGAAAACATCCTGACGTGGGACAGCGGGCCAGAGGGCAGGACACGGTCTACAGCATCG  
AGTATAAGACGTACGGAGAGAGGGACTGGGTGGCAAAGAAGGGCTGTCAGCGGATCACCCGGA  
AGTCCTGCAACCTGACGGTGGAGACGGGCAACCTCACGGAGCTCTACTATGCCAGGGTACCCGCT  
GTCAGTGCAGGAGGCGGTCAGCCACCAAGATGACTGACAGGTTGAGCTCTCTGCAGCACACT  
ACCCTCAAGCCACCTGATGTGACCTGTATCTCCAAAGTGAGATCGATTGAGATGATTGTTTCAT  
CCTACCCCCACGCCAATCCGTGCAGGCGATGGCCACCGGCTAACCTGGAAGACATCTTCCAT  
GACCTGTTCTACCACTTAGAGCTCCAGGTCAACCGCACCTACCAAATGCACCTTGGAGGGAAG  
CAGAGAGAATATGAGTTCTTCGGCCTGACCCCTGACACAGAGTTCCCTTGGCACCATCATGATT  
TGCGTTCCACCTGGGCCAAGGAGAGTGCCCCCTACATGTGCCGAGTGAAGACACTGCCAGAC  
CGGACATGGACCTACTCCTTCTCCGGAGCCTTCCTGTTCTCCATGGGCTTCCTCGTCGCAGTA  
CTCTGCTACCTGAGCTACAGATATGTACCAAGCCGCTGCACCTCCCAACTCCCTGAACGTC  
CAGCGAGTCTGACTTTCAGCCGCTGCGCTTCATCCAGGAGCACGTCCTGATCCCTGTCTTT  
GACCTCAGCGGCCCCAGCAGTCTGGCCCAGCCTGTCCAGTACTCCCAGATCAGGGTGTCTGGA  
CCCAGGGAGCCCGCAGGAGCTCCACAGCGGCATAGCCTGTCCGAGATCACCTACTTAGGGCAG  
CCAGACATCTCCATCCTCCAGCCCTCCAACGTGCCACCTCCCCAGATCCTCTCCCCACTGTCC  
TATGCCCCAAACGCTGCCCCCTGAGGTGCGGGCCCCCATCCTATGCACCTCAGGTGACCCCCGAA  
GCTCAATTCCCATTCTACGCCCCACAGGCCATCTCTAAGGTCCAGCCTTCCTCCTATGCCCCCT  
CAAGCCACTCCGGACAGCTGGCCTCCCTCCTATGGGGTATGCATGGAAGGTTCTGGCAAAGAC  
TCCCCCACTGGGACACTTTCTAGTCCTAAACACCTTAGGCCTAAAGGTCAGCTTCAGAAAGAG  
CCACCAGCTGGAAGCTGCATGTTAGGTGGCCTTTCTCTGCAGGAGGTGACCTCCTTGGCTATG  
GAGGAATCCCAAGAAGCAAAATCATTGCACCAGCCCCCTGGGGATTTGCACAGACAGAACATCT  
GACCCAAATGTGCTACACAGTGGGGAGGAAGGGACACCACAGTACCTAAAGGGCCAGCTCCCC  
CTCCTCTCCTCAGTCCAGATCGAGGGCCACCCCATGTCCCTCCCTTTGCAACCTCCTTCCGGT  
CCATGTTCCCCCTCGGACCAAGGTCCAAGTCCCTGGGGCCTGCTGGAGTCCCTTGTGTGTCCC  
AAGGATGAAGCCAAGAGCCCAGCCCCCTGAGACCTCAGACCTGGAGCAGCCCACAGAACTGGAT  
TCTCTTTTTCAGAGGCCTGGCCCTGACTGTGCAGTGGGAGTCTTGAGGGGAATGGGAAAGGCTT  
GGTGCTTCCTCCCTGTCCCTACCCAGTGTACATCCTTGGCTGTCAATCCCATGCCTGCCCAT  
GCCACACACTCTGCGATCTGGCCTCAGACGGGTGCCCTTGAGAGAAGCAGAGGGAGTGGCATG  
CAGGGCCCCCTGCCATGGGTGCGCTCCTCACCGGAACAAAGCAGCATGATAAGGACTGCAGCGG  
GGGAGCTCTGGGGAGCAGCTTGTGTAGACAAGCGCGTGCTCGCTGAGCCCTGCAAGGCAGAAA  
TGACAGTGCAAGGAGGAAATGCAGGGAAACTCCCGAGGTCCAGAGCCCCACCTCCTAACACCA  
TGGATTCAAAGTGCTCAGGGAATTTGCCTCTCCTTGCCCCATTCTTGCCAGTTTCACAATCT  
AGCTCGACAGAGCATGAGGCCCCCTGCCTCTTCTGTCAATTGTTCAAAGGTGGGAAGAGAGCCTG  
GAAAAGAACCAGGCCTGGAAAAGAACCAGAAGGAGGCTGGGCAGAACCAGAACACCTGCACT  
TCTGCCAAGGCCAGGGCCAGCAGGACGGCAGGACTCTAGGGAGGGGTGTGGCCTGCAGCTCAT  
TCCCAGCCAGGGCAACTGCCTGACGTTGCACGATTTGAGCTTCATTCTCTGATAGAACAAAG  
CGAAATGCAGGTCCACCAGGGAGGGAGACACACAAGCCTTTTCTGCAGGCAGGAGTTTCAGAC  
CCTATCCTGAGAATGGGGTTTGAAAGGAAGGTGAGGGCTGTGGCCCCCTGGACGGGTACAATAA  
CACACTGTACTGATGTCACAACCTTTGCAAGCTCTGCCTTGGGTTGAGCCCATCTGGGCTCAA  
TTCCAGCCTCACCCTCACAAGCTGTGTGACTTCAAACAAATGAAATCAGTGCCCAGAACCTC  
GGTTTCTCATCTGTAATGTGGGGATCATAACACCTACCTCATGGAGTTGTGGTGAAGATGAA  
ATGAAGTCATGTCTTTAAAGTGCTTAATAGTGCCTGGTACATGGGCAGTGCCCAATAAACGGT  
AGCTATTTAAAAA

165/168

**FIGURE 165**

TGGCCTACTGGAAAAAAAAAAAAAAAAAAAAAAAAAGTCACCCGGGCCCCGCGGTGGCCACAACAT  
GGCTGCGGGCGCCGGGGCTGCTCTTCTGGCTGTTTCGTGCTGGGGGCGCTCTGGTGGGTCCCGGG  
CCAGTCGGATCTCAGCCACGGACGGCGTTTCTCGGACCTCAAAGTGTGCGGGGACGAAGAGTG  
CAGCATGTTAATGTACCGTGGGAAAGCTCTTGAAGACTTCACGGGGCCCTGATTGTCGTTTTGT  
GAATTTTAAAAAAGGTGACGATGTATATGTCTACTACAACTGGCAGGGGGGATCCCTTGA  
TTGGGCTGGAAGTGTTGAACACAGTTTTGGATATTTTCCAAAAGATTTGATCAAGGTACTTCA  
TAAATACACGGAAGAAGAGCTACATATTCCAGCAGATGAGACAGACTTTGTCTGCTTTGAAGG  
AGGAAGAGATGATTTTAATAGTTATAATGTAGAAGAGCTTTTAGGATCTTTGGAAGTGGAGGA  
CTCTGTACCTGAAGAGTCGAAGAAAGCTGAAGAAGTTTCTCAGCACAGAGAGAAATCTCCTGA  
GGAGTCTCGGGGGCGTGAAGTTGACCTGTGCCTGAGCCCGAGGCATTCAGAGCTGATTCAGA  
GGATGGAGAAGGTGCTTTCTCAGAGAGCACCGAGGGGCTGCAGGGACAGCCCTCAGCTCAGGA  
GAGCCACCCTCACACCAGCGGTCCTGCGGCTAACGCTCAGGGAGTGCAGTCTTCGTTGGACAC  
TTTTGAAGAAATTCTGCACGATAAATTGAAAGTGCCGGGAAGCGAAAGCAGAACTGGCAATAG  
TTCTCCTGCCTCGGTGGAGCGGGAGAAGACAGATGCTTACAAAGTCCTGAAAACAGAAATGAG  
TCAGAGAGGAAGTGGACAGTGCCTTATTATTACAGCAAAGGATTTTCGTTGGCATCAAATCT  
AAGTTTGTTTTACAAAGATTGTTTTTTAGTACTAAGCTGCCTTGGCAGTTTGCATTTTTGAGCC  
AAACAAAATATATTATTTTCCCTTCTAAGTAAAAAAAAAAAAAAAAAAAAA

167/168

**FIGURE 167**

CCAGGACCAGGGCGCACCGGCTCAGCCTCTCACTTGTCAGAGGCCGGGGAAGAGAAGCAAAGC  
GCAACGGTGTGGTCCAAGCCGGGGCTTCTGCTTCGCCTCTAGGACATACACGGGACCCCTAA  
CTTCAGTCCCCCAAACGCGCACCCCTCGAAGTCTTGAAGTCCAGCCCCGCACATCCACGCGCGG  
CACAGGCGCGGCAGGCGGCAGGTCCCGGCCGAAGGCGATGCGCGCAGGGGGTTCGGGCAGCTGG  
GCTCGGGCGGCGGGAGTAGGGCCCCGGCAGGGAGGCAGGGAGGCTGCATATTCAGAGTCGCGGG  
CTGCGCCCTGGGCAGAGGCCGCCCTCGCTCCACGCAACACCTGCTGCTGCCACCGCGCGCCGGA  
TGAGCCGCGTGGTCTCGCTGCTGCTGGGCGCCGCGCTGCTCTGCGGCCACGGAGCCTTCTGCC  
GCCGCGTGGTCAGCGGCCAAAAGGTGTGTTTTGCTGACTTCAAGCATCCCTGCTACAAAATGG  
CCTACTTCCATGAACTGTCCAGCCGAGTGAGCTTTCAGGAGGCACGCCTGGCTTGTGAGAGTG  
AGGGAGGAGTCCTCCTCAGCCTTGAGAATGAAGCAGAACAGAAGTTAATAGAGAGCATGTTGC  
AAAACCTGACAAAACCCGGGACAGGGATTTCTGATGGTGATTTCTGGATAGGGCTTTGGAGGA  
ATGGAGATGGGCAAACATCTGGTGCTGCCCAGATCTCTACCAGTGGTCTGATGGAAGCAATT  
CCCAGTACCGAACTGGTACACAGATGAACCTTCCTGCGGAAGTGAAAAGTGTGTTGTGATGT  
ATCACCACCAACTGCCAATCCTGGCCTTGGGGGTCCCTACCTTTACCAGTGGAAATGATGACA  
GGTGTAACATGAAGCACAATTATATTTGCAAGTATGAACCAGAGATTAATCCAACAGCCCCTG  
TAGAAAAGCCTTATCTTACAAATCAACCAGGAGACACCCATCAGAATGTGGTTGTTACTGAAG  
CAGGTATAATTCCCAATCTAATTTATGTTGTTATACCAACAATACCCCTGCTCTTACTGATAC  
TGGTTGCTTTTGGAACCTGTTGTTTCCAGATGCTGCATAAAAAGTAAAGGAAGAACAAAATA  
GTCCAAACCAGTCTACACTGTGGATTTCAAAGAGTACCAGAAAAGAAAGTGGCATGGAAGTAT  
AATAACTCATTGACTTGGTTCCAGAATTTTGTAATTCTGGATCTGTATAAGGAATGGCATCAG  
AACAAATAGCTTGGAATGGCTTGAAATCACAAAGGATCTGCAAGATGAACTGTAAGCTCCCCCT  
TGAGGCCAAATATTAAAGTAATTTTTATATGTCTATTATTTTCAATTTAAAGAATATGCTGTGCTA  
ATAATGGAGTGAGACATGCTTATTTTGCTAAAGGATGCACCCAACTTCAAACCTTCAAGCAAA  
TGAAATGGACAATGCAGATAAAGTTGTTATCAACACGTCCGGGAGTATGTGTGTTAGAAGCAAT  
TCCTTTTATTTCTTTCACCTTTCATAAGTTGTTATCTAGTCAATGTAATGTATATTGTATTGA  
AATTTACAGTGTGCAAAAGTATTTTACCTTTGCATAAGTGTGTTGATAAAAATGAACTGTTCTA  
ATATTTATTTTATGGCATCTCATTTTTCAATACATGCTCTTTTGATTAAAGAACTTATTAC  
TGTGTCAACTGAATTCACACACACACAAATATAGTACCATAGAAAAAGTTTGTGTTTCTCGAA  
ATAATTCATCTTTCAGCTTCTCTGCTTTTGGTCAATGTCTAGGAAATCTCTTCAGAAATAAGA  
AGCTATTTTATTAAGTGTGATATAAACCTCCTCAAACATTTTACTTAGAGGCAAGGATTGTCT  
AATTTCAATTGTGCAAGACATGTGCCTTATAATTATTTTAGCTTAAATTAACAGATTTTG  
TAATAATGTAACCTTGTGTTAATAGGTGCATAAACACTAATGCAGTCAATTTGAACAAAAGAAGT  
GACATACACAATATAAATCATATGTCTTCACACGTTGCCTATATAATGAGAAGCAGCTCTCTG  
AGGGTTCTGAAATCAATGTGGTCCCTCTCTTGCCCACTAAACAAAGATGGTTGTTTCGGGGTTT  
GGGATTGACACTGGAGGCAGATAGTTGCAAAGTTAGTCTAAGGTTTCCCTAGCTGTATTTAGC  
CTCTGACTATATTAGTATACAAAGAGGTCATGTGGTTGAGACCAGGTGAATAGTCACTATCAG  
TGTGGAGACAAGCACAGCACACAGACATTTTAGGAAGGAAAGGAACACGAAATCGTGTGAAA  
ATGGGTTGGAACCCATCAGTGATCGCATATTCATTGATGAGGGTTTGCTTGAGATAGAAAATG  
GTGGCTCCTTTCTGTCTTATCTCCTAGTTTCTTCAATGCTTACGCCTTGTTCTTCTCAAGAGA  
AAGTTGTAACCTCTCTGGTCTTCATATGTCCCTGTGCTCCTTTTAACCAAATAAAGAGTTCCTG  
TTTCTGGGGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number  
**WO 01/16318 A3**

(51) International Patent Classification<sup>7</sup>: C12N 15/12,  
C07K 14/47, 14/705, G01N 33/53, C12N 15/62, C07K  
16/18

(21) International Application Number: PCT/US00/23328

(22) International Filing Date: 24 August 2000 (24.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
PCT/US99/20111

1 September 1999 (01.09.1999) US

PCT/US99/21090 15 September 1999 (15.09.1999) US

60/169,495 7 December 1999 (07.12.1999) US

60/170,262 9 December 1999 (09.12.1999) US

60/175,481 11 January 2000 (11.01.2000) US

PCT/US00/04341 18 February 2000 (18.02.2000) US

PCT/US00/04342 18 February 2000 (18.02.2000) US

PCT/US00/04414

PCT/US00/05601

60/187,202

60/191,007

PCT/US00/08439

60/199,397

PCT/US00/14042

60/209,832

22 February 2000 (22.02.2000) US

1 March 2000 (01.03.2000) US

3 March 2000 (03.03.2000) US

21 March 2000 (21.03.2000) US

30 March 2000 (30.03.2000) US

25 April 2000 (25.04.2000) US

22 May 2000 (22.05.2000) US

5 June 2000 (05.06.2000) US

(71) Applicant (for all designated States except US): GENEN-  
TECH, INC. [US/US]; 1 DNA Way, South San Francisco,  
CA 94080-4990 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): EATON, Dan,  
L. [US/US]; 75 Knight Drive, San Rafael, CA 94901  
(US). FILVAROFF, Ellen [US/US]; 538 18th Avenue,  
San Francisco, CA 94121 (US). GERRITSEN, Mary,  
E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402  
(US). GODDARD, Audrey [CA/US]; 110 Congo Street,  
San Francisco, CA 94131 (US). GODOWSKI, Paul,  
J. [US/US]; 2627 Easton Drive, Burlingame, CA 94010  
(US). GRIMALDI, Christopher, J. [US/US]; 1434 36th

[Continued on next page]

(54) Title: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

<subunit 1 of 1, 266 aa, 1 stop

<MW: 29766, pI: 8.39, NX(S/T): 0

MWWFQQLSFLPSALVIWTSAAFI FSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNIA  
AVLCIATIIYVRYKQVHALSPEENVIIKLNKAGLVGLSCLGLSIVANFQKTTLFAAHVSGAV  
LTFGMGSLYMFVQTILSYQMOPKIHGKQVFWIRLLLVIWCGVSALSMLTCSVLHSGNFGTDL  
EQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGFFLTYYIRDFQKISLRVEANLHGLTYDTAPC  
PINNERTRLLSRDI

Important features:

Type II transmembrane domain:  
amino acids 13-33

Other Transmembrane domains:

amino acids 54-73, 94-113, 160-180, 122-141

N-myristoylation sites.

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

(57) Abstract: The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

WO 01/16318 A3



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/23328

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 C07K14/705 G01N33/53 C12N15/62  
C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 25825 A (BOUGUELERET LYDIE ; GENSET SA (FR); DUCLERT AYMERIC (FR); DUMAS MIL) 27 May 1999 (1999-05-27) the whole document	1-20
X	WO 99 24836 A (ENDRESS GREGORY A ; HUMAN GENOME SCIENCES INC (US); FENG PING (US);) 20 May 1999 (1999-05-20) the whole document	1-20
A	EP 0 834 563 A (SMITHKLINE BEECHAM CORP) 8 April 1998 (1998-04-08) the whole document	
A	WO 97 07198 A (GENETICS INST) 27 February 1997 (1997-02-27) the whole document	
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

24 January 2001

Date of mailing of the international search report

23.04.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Smalt, R.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/23328

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 35-38, in as far as they pertain to in vivo methods, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-20 (all partially).

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: 1-20, all partially

PRO180: nucleic acid with seq.ID.1, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.2 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.2 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide.

2. Claims: Inventions 2-76: claims 1-20, all partially

Subject matter as defined for invention 1, but related to the respective nucleic acid/polypeptide sequences of:

2. PRO218, represented by seq.ID.s 3 and 4,
3. PRO263, represented by seq.ID.s 5 and 6,
4. PRO295, as represented by seq.ID's 7 and 8,
5. PRO874, as represented by seq.ID's 9 and 10,
6. PRO300, as represented by seq.ID's 11 and 12,
7. PRO1864, as represented by seq.ID's 13 and 14,
8. PRO1282, as represented by seq.ID's 15 and 16,
9. PRO1063, as represented by seq.ID's 17 and 18,
10. PRO1773, as represented by seq.ID's 19 and 20,
11. PRO1013, as represented by seq.ID's 21 and 22,
12. PRO937, as represented by seq.ID's 23 and 24,
13. PRO842, as represented by seq.ID's 25 and 26,
14. PRO1180, as represented by seq.ID's 27 and 28,
15. PRO831, as represented by seq.ID's 29 and 30,
16. PRO1115, as represented by seq.ID's 31 and 32,
17. PRO1277, as represented by seq.ID's 33 and 34,
18. PRO1074, as represented by seq.ID's 35 and 36,
19. PRO1344, as represented by seq.ID's 37 and 38,
20. PRO1136, as represented by seq.ID's 39 and 40,
21. PRO1109, as represented by seq.ID's 41 and 42,
22. PRO1003, as represented by seq.ID's 43 and 44,
23. PRO1138, as represented by seq.ID's 45 and 46,
24. PRO994, as represented by seq.ID's 47 and 48,
25. PRO1069, as represented by seq.ID's 49 and 50,
26. PRO1411, as represented by seq.ID's 51 and 52,
27. PRO1129, as represented by seq.ID's 53 and 54,
28. PRO1027, as represented by seq.ID's 55 and 56,
29. PRO1106, as represented by seq.ID's 57 and 58,
30. PRO1291, as represented by seq.ID's 59 and 60,
31. PRO3573, as represented by seq.ID's 61 and 62,
32. PRO3566, as represented by seq.ID's 63 and 64,
33. PRO1098, as represented by seq.ID's 65 and 66,
34. PRO1158, as represented by seq.ID's 67 and 68,
35. PRO1124, as represented by seq.ID's 69 and 70,

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

represented in seq.ID.156 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.156 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO10272 using its interaction with PRO5801 (seq.ID.158), method for linking a bioactive molecule to a cell expressing PRO10272 through the use of PRO5801, and method of modulating at least one activity of said cell thereby.

5. Claims: Invention 78: claims 1-3,5-12,14-38, all partially

PRO20110: nucleic acid with seq.ID.159, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.160 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.160 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO20110 using its interaction with PRO20040 (seq.ID.162), method for linking a bioactive molecule to a cell expressing PRO20110 through the use of PRO20040, and method of modulating at least one activity of said cell thereby.

6. Claims: Invention 79: claims 1-3,5-12,14-38, all partially

PRO10096: nucleic acid with seq.ID.153, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.154 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.154 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO10096 using its interaction with PRO20233 (seq.ID.164), method for linking a bioactive molecule to a cell expressing PRO10096 through the use of PRO20233, and method of modulating at least one activity of said cell thereby.

7. Claims: Invention 80: claims 1-3,5-12,14-38, all partially

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## 10. Claims: Invention 83: claims 1-3,5-12,14-38, all partially

PR020233: nucleic acid with seq.ID.163, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.164 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.164 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PR020233 using its interaction with PR010096 (seq.ID.154), method for linking a bioactive molecule to a cell expressing PR020233 through the use of PR010096, and method of modulating at least one activity of said cell thereby.

## 11. Claims: Invention 84: claims 1-3,5-12,14-38, all partially

PR01890: nucleic acid with seq.ID.167, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.168 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.168 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PR01890 using its interaction with PR019679 (seq.ID.166), method for linking a bioactive molecule to a cell expressing PR01890 through the use of PR019679, and method of modulating at least one activity of said cell thereby.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/23328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0073454 A		AU 2883600 A	28-09-2000
		WO 0053756 A	14-09-2000
		WO 0078961 A	28-12-2000
		WO 0104311 A	18-01-2001
		AU 1749800 A	04-10-2000
		AU 1749900 A	12-07-2000
		AU 2399300 A	28-09-2000
		AU 3107000 A	19-06-2000
		WO 0105972 A	25-01-2001
		WO 0032778 A	08-06-2000
		WO 0055319 A	21-09-2000
		WO 0037638 A	29-06-2000
		WO 0105836 A	25-01-2001
		WO 0053751 A	14-09-2000
		WO 0077037 A	21-12-2000
		WO 0109327 A	08-02-2001
		WO 0075317 A	14-12-2000
		AU 5922999 A	03-04-2000
		WO 0118210 A	15-03-2001
		WO 0116318 A	08-03-2001
		WO 0119987 A	22-03-2001
		AU 6498499 A	03-04-2000
		WO 0119991 A	22-03-2001
		AU 2224800 A	28-09-2000
		AU 2596700 A	28-09-2000
		AU 3107700 A	28-09-2000
		WO 0053754 A	14-09-2000
		WO 0053750 A	14-09-2000
		AU 2474700 A	19-06-2000